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"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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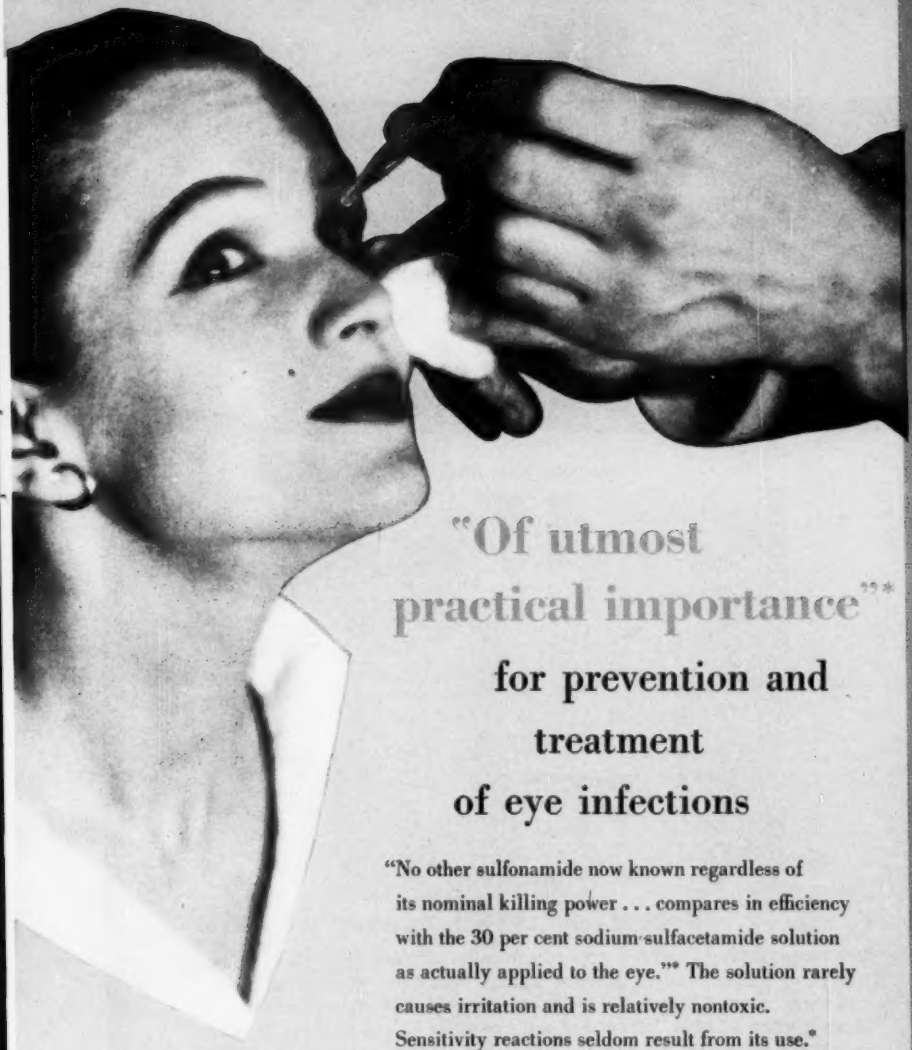

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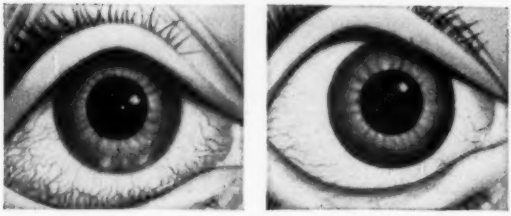

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1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* **45**:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* **34**:361, March 1951.

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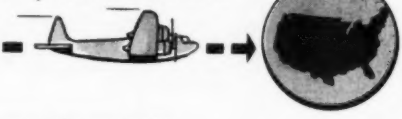

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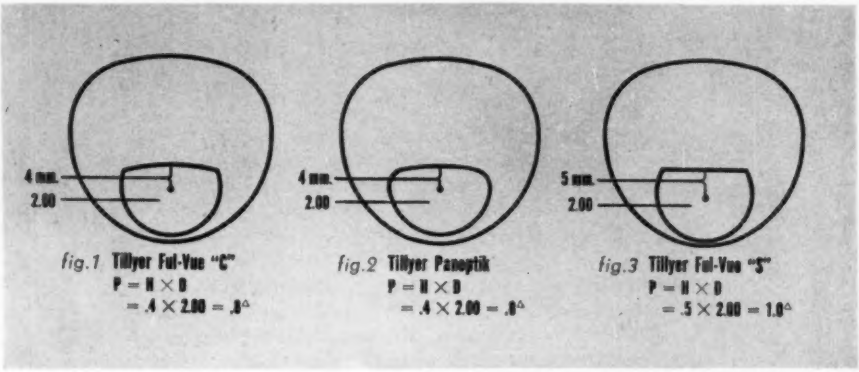

fig.1 **Tillyer Ful-Vue "C"**
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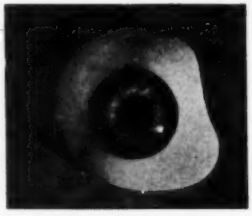

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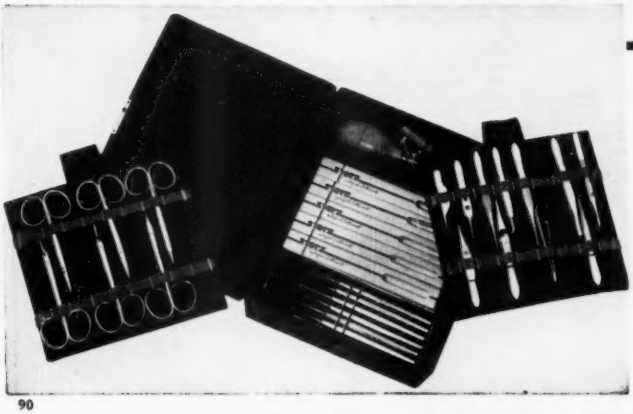

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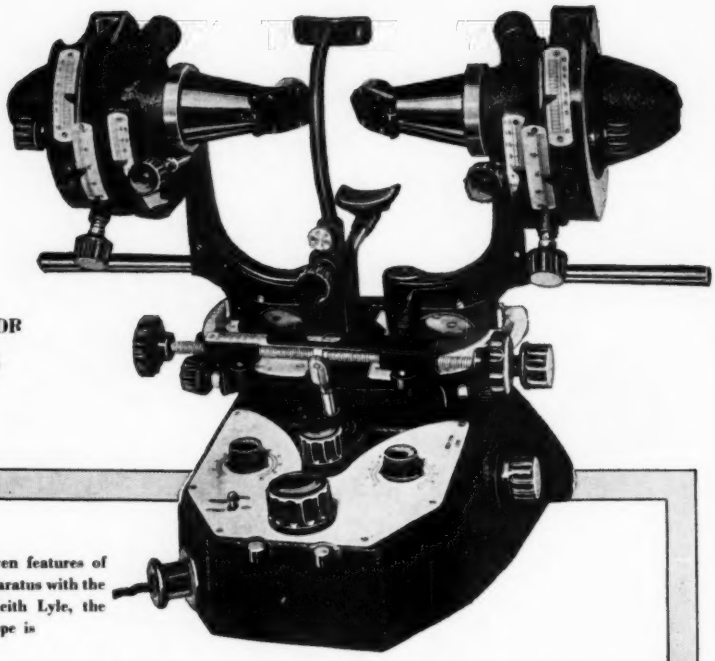

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RELATION OF HEREDITARY OPTIC ATROPHY (LEBER) TO OTHER FAMILIAL DEGENERATIVE DISEASES OF CENTRAL NERVOUS SYSTEM

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THIS REVIEW was undertaken to determine the nature of the relationship of Leber's hereditary optic atrophy to the other heredodegenerative diseases of the nervous system. It is well known that hereditary optic atrophy has often occurred in conjunction with Marie's hereditary cerebellar ataxia of varying degrees of severity. It is little known that Leber's atrophy may occur with the familial ataxia of Friedreich and with the hereditary spastic paraplegia of Strümpell, the Charcot-Marie-Tooth peroneal muscular atrophy, and the hypertrophic neuritis of Dejerine and Sotta. Other syndromes have recently been added to this impressive group.

A brief diagrammatic sketch of the neurological lesions and nomenclature involved will serve as a review of these confusing syndromes. They are usually discussed as separate nervous diseases, named after some neurologist and unrelated except by the fact that they all are hereditary. The present method of presentation was first used in a paper by Aring and Cobb.[1] It aims to give the biological relationship of these syndromes, at least from the anatomical standpoint. From the diagram (Figure) it can be seen that many discrete degenerative lesions are found in the spinal cord and brain, affecting certain systems. These are true system diseases and are illustrated as affecting the anterior roots, the anterior horn cells, and the pyramidal, cerebellar, and dorsal (long afferent) tracts. In the diagram of the brain degenerative lesions are indicated in the cerebellum and optic nerves. Various combinations occur that are expressed clinically in different syndromes; these have often been named after the neurologist who described them. Just what the hereditary disorder (genotype) may be is unknown, but the combination of symptoms that develop are the clinical syndromes (phenotypes). Only the well-known syndromes are illustrated; other combinations are described in the text. It is to be expected that new combinations will be found and described by assiduous neurologists. It is hoped that they will not be hailed as new disease entities.

LEBER'S HEREDITARY OPTIC ATROPHY

The clinical picture of Leber's hereditary optic atrophy is fairly well defined, although opinions are divided on the question of pathogenesis. The disease has a sudden onset, usually at puberty. Vision deteriorates rapidly for a few weeks to

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1. Aring, C. D., and Cobb, S.: Muscular Atrophies and Allied Disorders, Medicine **14**:77, 1935.

several months, after which there may be a certain degree of improvement, with the condition remaining stationary thereafter. In the early stages the optic disks present the picture of retrobulbar neuritis, the condition evolving later into definite optic atrophy. Central scotomata are always present, with little, if any, peripheral constriction of the visual fields.

	PATHOLOGY	NOSOLOGY
	PYRAMIDAL TR. DORSAL TRACTS ?	FAM. SPASTIC PARALYSIS described by STRUMPELL JENDRASSIK FREUD
	DORSAL TRACTS ANT. ROOTS	HYPERTROPHIC NEURITIS described by DEJERINE SOTTAS
	DORSAL TRACTS ANT. HORN CELLS	PERONEAL MUSC. ATROPHY described by CHARCOT MARIE TOOTH
	ANT. ROOTS DORSAL TRACTS ? PYRAMIDAL ?	FAMILIAL AREFLEXIA described by ROUSSY LEVY
	DORSAL TRACTS CEREBELLAR * PYRAMIDAL * ANT. HORN CELLS	FAMILIAL ATAXIA described by FRIEDREICH
	CEREBELLUM CEREBELLAR TRACTS	FAMILIAL CEREBELLAR ATAXIA described by MARIE
	OPTIC NERVES CEREBELLUM CEREBELLAR TRACTS	OPTIC ATROPHY described by LEBER plus CEREBELLAR ATAXIA (FRUSTE) combination described by BEHR

Diagram showing degenerative lesions in the cerebellum and optic nerves in various hereditary diseases of the central nervous system.

The disease has a sex-linked recessive type of inheritance, being transmitted by females and predominantly affecting males. A certain number of cases, however, are known in which females are affected. There seems to be a different incidence of this disease among Orientals. Kawakami [2] described a Japanese family with 19

2. Kawakami, R.: Beiträge zur Vererbung der familiären Sehnervenatrophie, von Graefes Arch. Ophth. **116**:568, 1926.

males and 12 females affected in four generations. Of the 1,182 patients reported by Bell,[3] 863 were males and only 155 were females among the Europeans, as compared with 97 males and 67 females among the Japanese.

There are many theories as to the pathogenesis of this disorder. Fisher [4] believed that an inherited temporary disorder of the pituitary gland might, by enlargement of that organ, result in pressure on the chiasm and induce the symptoms of the disease. Hormuth's [5] theory was that affected persons are born with a weak papillomacular bundle and that the factor precipitating the onset of the disease is entirely unknown. Bird and McEachern [6] thought that the condition might be due to insufficient supply of the neurotrophic optic-nerve factor caused by a genetic fault involving the essential enzyme system. The most widely accepted theory concerning the origin of Leber's optic atrophy is that of a primary neuronic degeneration localized in the optic nerve. The presence of "neuritis" in the early stages, however, seems to be incompatible with the concept of the degenerative origin of the atrophy. Ferguson and Critchley [7] attempted to explain this phenomenon, assuming that (*a*) the products of degeneration in the optic nerve may themselves act as irritants, superimposing an inflammation, or that (*b*) the inherited abiotrophy of the optic nerve needs the intervention of a neighboring sepsis for the development of the neuritis and the consequent atrophy. No evidence, however, of any definite toxic factor has as yet been discovered. The tendency toward slight improvement in vision in Leber's optic atrophy, which might appear to argue against its degenerative origin, has been convincingly explained by Wilmer, cited by Merritt,[8] as being due to the patient's learning to accommodate himself to his central scotoma and to use the periphery of his retina to better advantage.

The first histopathological study of Leber's optic atrophy, reported by Rehsteiner [9] in 1930, demonstrated the atrophy of the ganglion cell layer and of the nerve fiber layer of the retina and the degeneration of sheaths and axons of the optic nerve, particularly those forming the papillomacular bundle. There was no evidence of any inflammatory process. Rehsteiner regarded the disease as a parenchymatous degeneration, i. e., an abiotrophy in Gowers' sense.

Ferguson and Critchley,[7] Androp,[10] and van Leeuwen and van Bogaert [11] regarded Leber's optic atrophy as a familial neuronic abiotrophy, limited in typical

3. Bell, J.: Hereditary Optic Atrophy (Leber's Disease), in The Treasury of Human Inheritance, London, Cambridge University Press, 1931, Vol. 2, Pt. 4.

4. Fisher, J. H.: Leber's Disease (Hereditary Optic Atrophy): A Suggestion as to Its Cause, Tr. Ophth. Soc. U. Kingdom **36**:298, 1916.

5. Hormuth, P.: Beiträge zur Lehre von den hereditären Sehnervenleiden, Hamburg, L. Voss, 1900, Vol. 5, p. 63.

6. Bird, A. V., and McEachern, D.: Leber's Hereditary Optic Atrophy in Canadian Family, Canad. M. A. J. **61**:376, 1949.

7. Ferguson, F. R., and Critchley, M.: Leber's Optic Atrophy and Its Relationship with Heredo-Familial Ataxias, J. Neurol. & Psychopath. **9**:120, 1928.

8. Merritt, H. H.: Hereditary Optic Atrophy (Leber's Disease), Arch. Neurol. & Psychiat. **24**:775, 1930.

9. Rehsteiner, K.: Die erste anatomische Untersuchung eines Falles von geschlectsgebundener hereditärer Sehnervenatrophie (Leberscher Krankheit), von Graefes Arch. Ophth. **125**:14, 1930.

10. Androp, S.: Leber's Primary Optic Atrophy with Other Central Nervous System Involvement, Psychiatric Quart. **15**:215, 1941.

11. van Leeuwen, A., and van Bogaert, L.: Sur l'atrophie optique hérédo-familiale compliquée (Behr), forme de passage de l'atrophie de Leber aux hérédo-ataxies, Monatsschr. Psychiat. u. Neurol. **105**:314, 1942.

cases to the optic nerve, which may, however, be accompanied by degeneration in other parts of the nervous system. Leber himself considered the disease described by him in 1871 [12] as a pure clinical entity, uncomplicated by any other morbid condition. He admitted, nevertheless, that some of his patients stemmed from what might be termed degenerative stock. In his original papers, he stated that in many of the affected families there occurred neurological appearances of minor degree, such as headaches, nervousness, palpitations, and weakness, so that these persons could be referred to the group of "neuropaths." Since that time other authors have reported symptoms of various neurological disorders in patients with Leber's optic atrophy. There are many contradictory opinions concerning the nature of these other neurological involvements found in association with Leber's optic atrophy. Some, like Duke-Elder,[13] regard their occurrence as purely incidental; others consider them part of the same degenerative process as that affecting the optic nerve.

ASSOCIATION WITH PES CAVUS, EPILEPSY, AND VARIOUS NEUROLOGICAL SIGNS

In addition to simple, uncomplicated heredofamilial optic atrophy, there are numerous cases in which the patient experiences headaches and giddiness, as reported by Bell.[3] Nettleship [14] described nine families with Leber's optic atrophy and epilepsy. Of six cases of Leber's disease described by Pines and Tron,[15] tremor of the hands, nystagmus, and increased tendon reflexes were present in three. Two patients of Taylor and Holmes [16] had vague pains and paresthesias in the legs, as well as some defect in bladder control. Ford [17] described a patient with Leber's optic atrophy, hyperactive tendon reflexes, dysarthria, slight diffuse muscular atrophy and rigidity, and lumbar lordosis. The brother of this patient had hyperactive tendon reflexes and patellar clonus. Merritt [8] reported a case of typical Leber's optic atrophy with clubfoot similar to those of Friedreich's ataxia. The mother of the patient likewise had clubfoot. There was also a history of visual disorder in three generations. This case raises the question whether one should regard pes cavus as a manifestation of the same heredodegenerative process as the optic nerve atrophy, or whether one is dealing merely with a coincidental association of two separate diseases. To illuminate these relationships, we have collected from the literature cases representing the transition from Leber's optic atrophy to the group of "heredodegenerative spinocerebellar degenerations" defined by Mollaret [18] as including Friedreich's

12. Leber, T.: Über hereditäre und congenital-angelagte Sehnervenleiden, von Graefes Arch. Ophth. **17**:249, 1871.

13. Duke-Elder, W. S.: Diseases of the Inner Eye, in Text-Book on Ophthalmology, Vol. 3, St. Louis, C. V. Mosby Company, 1940, pp. 2097-3470.

14. Nettleship, E.: Bowman Lecture: On Some Hereditary Diseases of the Eye, Tr. Ophth. Soc. U. Kingdom **39**:57, 1909.

15. Pines, I. L. J., and Tron, G.: Hereditäre Neuritis optica (Lebersche Sehnervenatrophie), Ztschr. ges. Neurol. u. Psychiat. **95**:762, 1925.

16. Taylor, J., and Holmes, G.: Two Families with Several Members in Each Suffering from Optic Atrophy, Tr. Ophth. Soc. U. Kingdom **33**:95, 1912-1913.

17. Ford, F.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Springfield, Charles C Thomas, Publisher, 1937.

18. Mollaret, P.: La maladie de Friedreich: Étude physico-clinique, Paris, A. Lahure, 1929. Guillain, G., and Mollaret, P.: Considérations cliniques et physiologiques sur la maladie de Friedreich: L'hérédodegénération spino-cérébelleuse, Presse méd. **41**:1417, 1933.

ataxia, cerebellar ataxia, and hereditary spastic paraplegia, and to which, in the opinion of Austregesilo,[19] peroneal muscular atrophy and hypertrophic neuritis also belong.

Thus, Immamura and Ichikawa [20] reported the cases of two Japanese siblings, a brother and sister, suffering from Leber's optic atrophy and tremor. Androp [10] described two brothers with Leber's disease and symptoms that were strongly suggestive of Friedreich's ataxia. Ferguson and Critchley [7] reported a family in which four of five siblings were affected with typical Leber's optic atrophy. The fifth child died at the age of 6 months of "curvature of the spine and convulsions." In all cases the optic atrophy appeared at puberty. One patient showed, in addition, some degree of mental deficit and epilepsy. The fourth patient manifested symptoms of pyramidal disease, ataxia, and loss of proprioceptive sensitivity. Her gait was slow and unsteady, with a broad base; there was a tendency to sway from one side to the other; all movements were jerky, and deep reflexes were brisker than normal. She had marked impairment of the sense of passive movement and position, as well as of vibration sense in both lower extremities. There was some speech disturbance. Both feet showed a slight degree of pes cavus. Ferguson and Critchley regarded this case as representing a definite connecting link between Leber's optic atrophy and the heredofamilial ataxias.

Collier [21] described a family in which grave optic atrophy occurred in five women in three generations. One also had loss of knee jerks and nystagmus. Her daughter had optic atrophy combined with symptoms reminiscent of Friedreich's ataxia, such as tremor of the hands, ataxia of the upper extremities, nodding tremors of the head, some loss of deep sensibility in the legs, loss of deep reflexes, a bilateral Babinski sign, and pes cavus.

ASSOCIATION WITH ABORTIVE HEREDITARY ATAXIA (BEHR)

From this group of cases, in which the visual symptoms were predominant over the neurological ones, we may pass to a heredofamilial optic atrophy associated, as a rule, with an abortive form of hereditary ataxia. The first six cases of this disease were described by Behr [22] in 1909 under the name of "complicated infantile heredofamilial optic atrophy." In all the patients symptoms went back to earliest childhood; there were bilateral optic atrophy with central scotoma, slight rigidity, hyperactive tendon reflexes, the Babinski sign and nystagmus, slight disturbance of coordination, a spastoataxic gait, and monotonous speech. There also existed some mental retardation and weakness of the bladder control. Behr regarded his cases as representing a transition form between Leber's optic atrophy and Strümpell's hereditary spastic paraplegia, on one side, and the heredoataxias, on the other.

19. Austregesilo, A.: Parentesco entre las atrophies musculares Charcot-Marie, Déjérine-Sottas e a doenca de Friedreich, Clin. neurol. **2**:56, 1932.

20. Immamura, S., and Ichikawa, K.: Atrophie optique familiale avec tremblement et déchéance intellectuelle, Rev. neurol. **26**:277, 1919.

21. Collier, J.: Two Members of a Family in Which Visual Defects and Loss of Knee-Jerks Have Occurred During Three Generations, Proc. Roy. Soc. Med., Vol. 6, Neurol. Sec., p. 64, 1912-1913.

22. Behr, C.: Die komplizierte, hereditärfamiliäre Optikusatrophie des Kindesalters, Monatsbl. Augenh. **7**:138, 1909.

Later Takashima [23] described six cases of the "Behr syndrome," establishing the stationary character of the disease in later life. More recently, van Leeuwen and van Bogaert [11] and Franceschetti [24] described families affected by this syndrome. The family reported by van Leeuwen and van Bogaert is of great importance in that it brings up the first known histopathological study of this curious affection. It is to be noted that, in addition to the symptoms of the Behr syndrome, the four affected siblings had pes cavus later, at about the age of 12 years. The optic atrophy in these members was said to present the picture of "retrobulbar neuritis." The mother of these patients, their grandfather, and several other members of the family in previous generations showed a discrete temporal optic atrophy, which appeared in adult life. The histopathological study of one of the children, who died of cerebral hemorrhage at the age of 11, revealed bilateral optic atrophy with degeneration of the retinogeniculate neurons, affecting mainly the papillomacular bundle, although extending well beyond it. In the spinal cord there was degeneration of the posterior columns and spinocerebellar tracts and gliosis of the pyramidal tracts, which could be followed up to the cervicobulbar region.

It is impossible to determine what type of optic atrophy caused the mild and isolated affection of the optic nerve observed in two generations of this family, which, in the third generation, evolved into a grave optic atrophy accompanied by abortive hereditary ataxia. The authors were inclined to regard it as Leber's optic atrophy, although the classic sign of central scotoma was in many cases missing. The inheritance was also not of the usual sex-linked recessive type, but was definitely dominant, and in the older branch two men transmitted the optic atrophy to both sexes. To support their view, the authors presented a critical review of known pedigrees of Leber's disease, drawing the conclusion that the question of the sex-linked recessive type of inheritance could not be definitely established and that there exist various transitions between the dominant, recessive, and intermediary inheritances.

In reviewing the preceding cases, Franceschetti [24] objected to the diagnosis of Leber's disease on the grounds that in most of them the central vision was normal, or only slightly impaired, whereas in Leber's optic atrophy the considerable loss of central vision is characteristic. He also believed that a simple dominant inheritance in this family constituted a sufficient argument against Leber's disease.

In our opinion, this hereditary optic atrophy, even if not identical, is, nevertheless, closely related to Leber's optic atrophy. The fact that, with the strengthening of the expressiveness and the penetration of the pathological gene, this isolated optic atrophy evolved into severe optic atrophy with ataxia indicated that there is a direct link between the hereditary optic atrophies and the hereditary ataxias.

ASSOCIATION WITH DEFINITE HEREDITARY ATAXIA

It is important to note that the optic atrophies seem to have a special affinity with the group of hereditary ataxias, being seen often in association with the cerebellar ataxia of Pierre Marie and, less frequently, with Friedreich's ataxia. They

23. Takashima, S.: Sechs Fälle der komplizierten hereditär-familiären Optikusatrophie des Kindesalter (Behr), Klin. Monatsbl. Augenh. **16**:714, 1913.

24. Franceschetti, A.: Le syndrome de Behr, ses rapports avec la maladie de Leber et les hérédoataxies, Ophthalmologica **107**:17, 1944.

are also encountered in cases of hereditary spastic paraplegia and, comparatively rarely, in cases of peroneal atrophy and hypertrophic neuritis. It is difficult, however, to evaluate the exact nature of these optic atrophies in view of the fact that in most reported cases only their presence is stated at the time of observation, without any pertinent data as to the mode of onset and progression. In her important study on the subject, van Leeuwen and associates [25] seemed to have isolated, from a sum total of observations, two more or less well-determined types of optic atrophy as appearing in association with the "heredodegenerative spinocerebellar degenerations": (*a*) an atrophy of "retrobulbar neuritis" type, and (*b*) a severe optic atrophy of early onset. There seems to exist also a third type, that of a global, slowly progressive optic atrophy. This, however, has not as yet been clearly defined.

One of the oldest and most detailed observations is that reported by Nonne in 1891.[26] The author described three brothers suffering from Marie's cerebellar ataxia with optic atrophy. Many other members of the family presented slight neurological symptoms, such as ocular or facial paresis. The younger brother, believed to be most severely affected, was not examined during life, but histopathological studies revealed degeneration of the optic nerves. In the second brother, the first neurological symptoms appeared at the age of 30. The oldest brother had had difficulty in walking since the age of 14, with gradual diminution of vision. At the age of 49 both optic disks were completely discolored. The pathological study of this case, reported in 1905,[27] demonstrated a grossly atrophied optic nerve; histologically the degeneration was predominant in the central and lower central bundles, which appeared to be much paler and more shrunken than the bundles situated farther at the periphery. The optic atrophy in this family seems to be of the global, slowly progressive type.

The retrobulbar neuritis seems to be much better defined and is characterized in the majority of cases by its stationary, or only slightly progressive, character in later life. The age of onset varies greatly from case to case. Central scotomata are usually present, and there is temporal discoloration of the optic disks. The peripheral regions of the visual fields are, in general, little affected.

The recent observation of van Leeuwen and van Bogaert [28] brings an interesting case of a 20-year-old woman with the cerebellar ataxia of Pierre Marie and optic atrophy of retrobulbar neuritis type. Some ataxia, together with some impairment of vision, appeared at the age of 3 years. However, a severe disturbance of central vision, with rapid progression of the cerebellar affection, did not appear until the age of 18. After this acute phase, of four months' duration, the ocular status remained stationary until the patient's death, at the age of 20. The optic disks in this case presented the picture of retrobulbar neuritis, with atrophy predominant

25. van Leeuwen, A.; Babel, J.; van Bogaert, L.; Franceschetti, A.; Klein, D., and Montandon: Des atteintes optiques, rétiniennes, et cochléaires dans les dégénérescences spino-ponto-cérébelleuse, Rev. oto-neuro-opht. **20**:1, 1948.

26. Nonne, M.: Über eine eigenthümliche familiäre Erkrankungsform des Centralnervensystems, Arch. Psychiat. **22**:283, 1891.

27. Nonne, M.: Ein weiterer anatomischer Befund bei einem Fall von familiärer Kleinhirnataxia, Arch. Psychiat. **39**:1225, 1905.

28. van Leeuwen, A. M., and van Bogaert, L.: Hereditary Ataxia with Optic Atrophy of the Retrobulbar Neuritis Type, and Latent Pallido-Luysian Degeneration, Brain **72**:340, 1949.

in the temporal zone and central scotomata. The pathological studies demonstrated symmetrical degeneration of both papillomacular bundles, which could be followed across the chiasm and into the external geniculate body. This pathological picture presents obvious analogies with the one reported by Nonne.

ASSOCIATION WITH SPASTIC PARALYSIS

Jendrássik [29] reported two sisters, 18 and 10 years old, respectively, who had spastic paralysis with optic atrophy of the retrobulbar type. The older girl was healthy until the age of 10 years, when divergent strabismus and slight spasticity in gait were noticed. At the age of 18 she had severe optic atrophy with central scotoma, the peripheral regions of the visual fields being almost intact. The color sense was greatly affected. The optic disks showed complete (global) discoloration. In the younger sister the affection started around the age of 9 years, when it was noted that her vision was failing and that she had difficulty in walking. The fundi showed pronounced optic nerve atrophy; her visual acuity was 1/5; the fields of vision were greatly reduced, but the child was still able to read and write. In this case the optic atrophy seems to be of the global type, not temporal, as is usually seen in retrobulbar neuritis.

ASSOCIATION WITH MUSCULAR ATROPHY AND HYPERTROPHIC NEURITIS

Schneider and Abeles [30] reported two brothers, aged 41 and 26, respectively, with Charcot-Marie-Tooth peroneal muscular atrophy and optic atrophy. The parents were first cousins. One sister was myopic. There was a vague history of a maternal grandaunt who became blind at 45 and of a paternal aunt with "very thin legs." In the older brother, vision started to fail at the age of 7 years and continued to fail up to adolescence, impairment becoming stationary in adult life. The difficulty in walking first appeared at the age of 12. At the age of 45 his visual acuity was 1/100. There was bilateral optic atrophy with central scotoma. In the younger brother, the clinical course of the optic nerve affection was very similar. The authors pointed out that the presence of central scotoma, with optic atrophy, as well as the stationary character of the disease in adult life, is analogous with the symptoms of Leber's optic atrophy. The early and insidious onset in this case, however, is in contrast with the sudden onset of Leber's disease at puberty.

Milhorat [31] reported two brothers, aged 32 and 41, respectively, with difficulty in walking and impaired vision since childhood. Wasting of the feet and calves was noticed at an early age (at 15 in the older brother). Muscular atrophy progressed gradually, until the appearance of "stork legs." The visual disturbance progressed steadily, and at the time the patients were examined both showed advanced atrophy of the optic disks, more pronounced in the temporal region. Both patients had nystagmus. Deep reflexes were reduced or absent. All extremities showed sensory defects of the stocking type. The peripheral nerves were found

29. Jendrássik, E.: Über Paralysis spastica; und über die vererbten Nervenkrankheiten in allgemeinen, Deutsches Arch. klin. Med. **58**:137, 1897.

30. Schneider, D., and Abeles, M.: Charcot-Marie-Tooth Disease with Primary Optic Atrophy: Report of Two Cases Occurring in Brothers, J. Nerv. & Ment. Dis. **85**:651, 1937.

31. Milhorat, A. T.: Studies in Diseases of Muscle: Progressive Muscular Atrophy of Peroneal Type Associated with Atrophy of the Optic Nerves: Report on a Family, Arch. Neurol. & Psychiat. **50**:279, 1943.

to be enlarged on palpation, but not to the degree usually seen in hypertrophic neuritis. Therefore the authors considered the diagnosis of Charcot-Marie-Tooth disease rather than Leber's disease. In reviewing these cases, however, van Leeuwen, as well as van Bogaert and associates [25] referred to them as cases of hypertrophic neuritis associated with optic atrophy. The sister of these patients was said to have suffered from a "disease resembling multiple sclerosis with bilateral optic atrophy."

PRECOCIOUS GRAVE OPTIC ATROPHY

In the family reported by van Leeuwen [25] the two siblings, a brother and sister 18 and 16 years old, respectively, had a particularly precocious and severe form of Friedreich's disease, associated with early and rapidly progressing optic atrophy. The difficulty in walking was noticed at the ages of 2½ and 3, respectively. The visual disturbance was noticed at the ages of 8½ and 6 years. At the age of 9 years the optic disks already showed a marked discoloration. The family described by Stewart [32] is of particular interest in that it brings the description of an unusually early form of cerebellar ataxia of Pierre Marie associated with precocious, perhaps even congenital, optic atrophy, which progressed very rapidly into almost complete blindness.

ASSOCIATION WITH AUDITORY NERVE ATROPHY

The clinical picture of this type of optic atrophy has been corroborated by histopathological study reported by Nyssen and van Bogaert.[33] These authors described two siblings, aged 11 and 9 years, respectively, with a familial degenerative disease which had never before been observed, and which they proposed to name "a systematic opticocochleodentate degeneration of familial type." This curious affection has since been included, by various European authors, in the group of "heredodegenerative spinocerebellar degenerations."

The disease appeared in the sister and brother at the ages of 2½ and 4 years, respectively, manifesting itself by nervousness and sudden diminution of vision, which evolved rapidly into complete optic atrophy and blindness. Funduscopy revealed retinal lesions in both patients. In the interval of about two years, a deficit of auditory functions appeared, progressing into complete deafness. The neurological involvement appeared later, in the form of a definite ataxospastic syndrome. In the girl the speech became slow and scanning in the terminal phase of the disease. The histopathological study of this patient revealed (*a*) diffuse and almost complete demyelination of the optic nerves, chiasm, and optic tracts; (*b*) a systematic degeneration of the primary and secondary auditory tracts, and (*c*) a symmetrical degeneration of dentate nuclei with degeneration of superior olives.

ASSOCIATION WITH TAPETORETINAL AND COCHLEAR DISORDERS

Brief mention should be made of the relationship of optic atrophies, tapetoretinal affections, and cochlear involvement as they appear in association with heredodegenerative diseases of the nervous system. In all probability, these manifestations represent the extensions of the basic process, as suggested by the "optico-

32. Stewart, P.: Familial Amaurotic Ataxic Paraplegia, Rev. Neurol. & Psychiat. **10**:357, 1912.

33. Nyssen, R., and van Bogaert, L.: La dégénérescence systématisée optico-cochléo-dentelée: (étude anatomoclinique d'un type familial), Rev. neurol. **2**:321, 1934.

cochleodentate degeneration" of Nyssen and van Bogaert.[33] This curious disorder seems to enter the range of "acousticoretinocerebrospinal heredopathias" of Hammerschlag,[34] one of his cases being that of a 12-year-old girl with deafness, mental deficit, retinitis pigmentosa, and cerebellar gait. It also bears a certain resemblance to the case of Clauss,[35] that of a 42-year-old woman with Marie's ataxia and a taint of the spastic paraplegia of Strümpell, associated with deafness of cochlear type and retinitis pigmentosa. The grandmother of this patient suffered also from impairment of vision and hearing with difficulty in walking.

Vitello[36] described two patients who had Marie's ataxia with atypical retinitis pigmentosa and deaf-mutism. An older sister had congenital kyphoscoliosis; another sister was partially deaf. A paternal uncle was mentally ill, and on the maternal side one cousin was a deaf-mute, another was deaf, and still another had oligophrenia. The two patients, brother and sister, 56 and 53 years old, respectively, presented congenital deaf-mutism, impairment of vision since childhood, and cerebellar ataxia since the age of 30. The brother presented the so-called retinitis pigmentosa sine pigmento; the sister showed slight atrophy of the optic disks and "dusty opacities" of the corpus vitreum, considered by the author to be due to primary retinitis pigmentosa.

The problem of coexistence of the tapetoretinal affections (primary degenerations of the retina associated with disorders of the pigmentary epithelium) with heredodegenerative diseases of the nervous system has received considerable attention in the foreign literature, having been studied extensively by Francheschetti and Klein.[37] The optic affections of this type have been observed in various combinations, either coexisting or alternating with optic atrophies in the same families, or appearing alone accompanying various types of hereditary spinocerebellar diseases.

In the family described by Piton and Tiffeneau[38] the mother had presented difficulty in walking and speech since the age of 38 and was known to have died blind. Her daughter, by her first marriage, had had Marie's ataxia since the age of 40, with bilateral optic atrophy and paralysis of the upward ocular movements. Her son, from her second marriage, had, in addition to the above symptoms, retinitis pigmentosa. In the remarkable family reported by Brown,[39] with 21 members afflicted with Marie's ataxia, 5 members were found to have optic atrophy, with two of them also manifesting distinct lesions of the retina. There was a history of visual disorders (night blindness) in five other members in three generations of

34. Hammerschlag, V.: Die Heredopathia acustica und ihr Erbung, zugleich eine Erläuterung einfacherer Mendelistischer Vorgänge, Wien. med. Wchnschr. **83**:1284; **83**:1319; 1933; **84**:93; **84**:119, **84**:288, **84**:319, **84**:345, 1934.

35. Clauss, O.: Über hereditäre cerebellare Ataxia in Verbindung mit Pigmentdegeneration der Retina (Retinitis pigmentosa) und Degeneration des N. cochlearis, Ztschr. ges. Neurol. u. Psychiat. **93**:294, 1924.

36. Vitello, A.: II Pisani, Gior. di patol. nerv. et ment. **59**:129, 1939.

37. (*a*) Franceschetti, A., and Klein, D.: Weiterer Beitrag zur Frage der genetischen Beziehungen zwischen der Friedreichschen Ataxie und den verschiedenen Formen der tapetoretinalen Degenerationen, Bull. schweiz. Akad. med. Wissensch. **2**:321, 1947. (*b*) van Leeuwen and others.[25]

38. Piton, J., and Tiffeneau, R.: Maladie familiale du type de l'hérédoataxia, Rev. neurol. **72**:774, 1940.

39. Brown, S.: On Hereditary Ataxia with Series of 21 Cases. Brain **15**:250, 1892.

the family. Lelong, Bertrand, and Lereboullet [40] reported a case of an 11-year-old girl who had atypical ataxia of Pierre Marie with progressive optic atrophy and limitation of lateral and vertical movements of the eye. Four years later the appearance of gross chorioretinitis with diffuse pigmentary deposits in the whole retina was noted. Mollaret and Cachin [41] described the case of a 41-year-old patient with a mild form of Friedreich's ataxia with optic atrophy and chorioretinitis. His sister was said to have an identical disease.

Kapuściński [42] reported the cases of three siblings in a family of 13 children. The two sisters, aged 30 and 14, respectively, and their brother, aged 17, were found to have Friedreich's ataxia with atypical pigmentary degeneration of the retina and progressive choroidal sclerosis. The disease appeared at about the age of 6 years, manifesting itself by day blindness, gradual impairment of vision, myopia, and nystagmus.

By far the most important of all reports in the literature is that of the Glaser family, described by Francheschetti and Klein,[37a] with 29 members suffering from Friedreich's ataxia, in 10 sets of siblings; 4 had juvenile macular degeneration, in 2 sets of siblings; 4 siblings had retinitis pigmentosa, and 2 had retinitis punctata albescens. In one of the collateral branches several members in four generations presented a dominant cochlear deafness. All the branches of this family were closely interrelated and descended from their common ancestor, Ludwig Glaser, who lived in the 16th century. It is unlikely that this common ancestor would have transmitted so many different mutations, and the authors were inclined to believe, rather, that these different affections were expressions of one pathological gene and represented a "familial alteration of a phenotype."

COMMENT

These various involvements demonstrate the wide extension of the basic heredodegenerative process. It is not limited to the central nervous system, but affects peripheral nerves, cranial nerves, cochlear, retina, and tapetum. Whether the skeletal changes, such as pes cavus and scoliosis, are hereditary changes of bone and muscle themselves, or whether they are secondary to the abnormal neural development, is not clear.

The clinical manifestations of the optic atrophies that appear in association with heredodegenerative diseases of the nervous system are of varying intensity. How can this variability be explained in view of possible relationships between these optic atrophies and the isolated hereditary optic atrophy of Leber? Some authors consider these optic atrophies to be one of the authentic manifestations of the heredodegenerative disease, its integral part; others consider it to be an association of two autonomous degenerative affections, hereditary spinocerebellar degeneration and Leber's optic atrophy (Schneider and Abeles [30]). The genetic aspect of this question presents one with a difficult point for discussion, as the mode of transmission

40. Lelong, M.; Bertrand, I., and Lereboullet, J.: L'affection dégénérative proche de l'hérédoataxie cérébelleuse avec atteinte du neurone moteur périphérique, Rev. neurol. **73**:360, 1941.

41. Mollaret, P., and Cachin, M.: La forme radiculocordonale postérieure de la maladie de Friedreich. Ses analogies avec la maladie de Roussy-Lévy, Rev. neurol. **2**:583, 1934.

42. Kapuściński, W.: Über familiäre Aderhautentartung mit ataktischen Störungen, Ber. ü. d. Versamml. deutsch. ophth. Gesellsch. **50**:13, 1934.

of these optic atrophies seems usually to correspond with the mode of inheritance of the particular hereditary degeneration with which they are associated (van Leeuwen and van Bogaert), whereas in Leber's optic atrophy the inheritance is supposed to be sex-linked recessive. In this respect the optic atrophies seem to behave as an integral part of the neurological disorder which they accompany and do not seem to represent true Leber's disease.

We have attempted, although with caution, to reconcile the seemingly incompatible views, assuming that the optic atrophies seen in association with neurological affections, although definitely not identical with Leber's disease, may, however, be regarded as products of evolution of the latter. We believe we have demonstrated the various stages of this process by presenting a series of cases with isolated hereditary optic atrophy, showing a gradual strengthening of the neurological component. For instance, it may increase to the manifestation of a severe hereditary ataxia. There is apparently no dividing line between the cases of "Behr's syndrome" and those reported as cases of Leber's optic atrophy with various neurological symptoms. The clinical picture of the Behr syndrome seems to be identical with that seen in typical Leber's optic atrophy as far as the appearance of retrobulbar neuritis in early stages is concerned; there are, also, the presence of central scotomata and the stationary character of the optic disorder in adult life. The early age of onset of the Behr optic atrophy seems to constitute the only difference from typical Leber's disease. In this respect Behr's optic atrophy seems to approximate "congenital" hereditary optic atrophy, which, as pointed out by van Leeuwen and van Bogaert, has never actually been observed at birth. In connection with the family Del,[11] recorded above, these authors were inclined to believe, contrary to the opinion of Stähli,[43] that the congenital Leber and Behr optic atrophies are in reality only different manifestations of the same pathological gene. A similar view had previously been expressed by Nettleship,[14] and later Julia Bell,[3] who considered "congenital" hereditary optic atrophies to be the same as those which occur in later life and come under the category of Leber's disease.

It is our opinion that the data collected in this paper indicate strongly that Leber's optic atrophy is an integral part of a hereditary degenerative disease of the nervous system. Like other parts of this complex disorder, it may appear alone or in combination with one, two, three, or more of the other neural degenerations. If alone, it is called "Leber's disease"; if combined with a few symptoms, it may be called "Behr's syndrome"; if found with severe spinocerebellar symptoms, it is looked upon as "Friedreich's ataxia with optic atrophy." The optic atrophy has been found in combination with many of the rarer manifestations of heredodegenerative nervous disease, for example, with degenerations of the cochlear nerve, the pyramidal tracts, the anterior horn cells, and the peripheral nerves. Whether the various syndromes are caused by several abnormal genes appearing in different combinations, or by one gene with varying potency, is a matter to be decided by genetic research.

43. Stähli, S.: Gibt es eine erbliche Sehnervenatrophie ausser der Leberschen Atrophie? Arch. Augenh. **104**:222, 1931.

NEW TREATMENT FOR CALCIFIC CORNEAL OPACITIES

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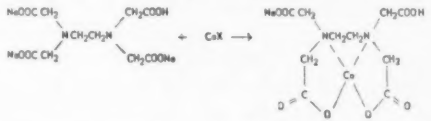
IN THIS paper a clinically useful method for dissolving calcific corneal opacities by means of a solution of the neutral sodium salt of ethylenediamine tetraacetic acid is reported.

Treatment with a solution of this material is appropriate for corneal opacities which consist of calcific deposits in the anterior layers of the stroma or in the epithelium. This type of corneal opacity may be exogenous, resulting from a lime burn, or may be endogenous in the band keratopathies associated with protracted uveitis, hypercalcemia, or phthisis bulbi. No effect from treatment with this solution is to be expected in opacities which are noncalcific, such as result from edema, infiltration with inflammatory cells, scarring, or vascularization.[1]

The purpose of treatment for removal of calcific corneal opacities may be to improve vision when the opacities are axially situated or to relieve discomfort when calcific particles are being spontaneously extruded through the corneal epithelium.

The substance (EDTA) which is employed for the treatment forms a soluble compound with calcium, holding the calcium more securely in solution than any previously known solubilizing agent. This substance is widely employed industrially under the trade names "versene" [2] and "sequestrene" [2] for keeping calcium (and other metals) in solution in unreactive form. Solutions of the same substance have been applied medically to the dissolution of calcific kidney stones and in experimental treatment of lead poisoning. The reaction between calcium compounds and neutral EDTA is shown in the accompanying formula.



EDTA and its inorganic salts are water-soluble but lack lipid solubility. This material, therefore, does not penetrate the corneal epithelium, and unless a calcific

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1. Some clearing effect would be expected in corneal opacities due to other metallic elements, e. g., barium and lead; but no actual investigation of these has yet been made. Initial trials on corneal rust rings from steel or iron foreign bodies have been disappointing.

2. These commercial preparations are much more concentrated and much more alkaline than the solution to be recommended for treatment of the cornea.

opacity extends to the surface it is necessary to remove the epithelium before dissolution of the calcific deposit is possible. EDTA has little toxicity when taken orally and when given intravenously is toxic only when administered in sufficient quantity to lower the blood calcium concentration. On the skin no sensitization reaction has been observed, although the compound has been employed in considerable amount in soaps and cosmetics. EDTA has been found to be well tolerated by the eye when applied to the intact or the denuded cornea under the conditions of concentration, pH, and time which are to be described for treatment of calcific corneal opacities.

For treatment of calcified corneas, the selection of EDTA from among various potential solubilizing agents has been based on a rather qualitative comparison of irritancy and solubilizing activity. For the establishment with certainty of the best selection, a quantitative comparison of penetrability, toxicity, and solubilizing activity would be required, and this was beyond the aims of this report. For the present purpose of simply choosing conditions for a practical and effective treatment, substances considered in addition to EDTA were ammonium salts, citrate, and a special phosphate (sodium hexametaphosphate; "calgon"). Solutions of ammonium salts, neutral ammonium tartrate in particular, have long been known to have the capacity of dissolving old calcific corneal opacities, but the rate of dissolution has been so slow and the application so discomforting to the patient that this form of treatment has generally been regarded as unsatisfactory. The ammonium salts were therefore dropped from further consideration on this basis. Solutions of sodium citrate, on the other hand, exhibit little irritancy to the cornea, actually less than EDTA at equal concentration, but the calcium-solubilizing activity of sodium citrate at a moderate concentration (5%) was found to be inadequate for removal of calcific opacities within a reasonable period. Citrate was therefore not considered to be practical. "Calgon" was found experimentally to be tolerated by the cornea approximately as well as EDTA, but "calgon" caused injury to conjunctival blood vessels at a lower concentration than did EDTA. Furthermore, "calgon" tested experimentally in vitro was found to be inferior to EDTA in calcium-solubilizing activity. For these reasons "calgon" appeared to be in a disadvantageous position. EDTA, on the other hand, is satisfactorily tolerated by the eye except at high concentrations, and it has sufficient calcium-solubilizing activity to permit removal of opacities within a reasonable time (as will be seen in the case reports) at concentrations which are essentially noninjurious to both experimental animals and patients.

INVESTIGATION OF TOXICITY TO THE EYE

Tests of neutral solutions of EDTA at various concentrations were made on rabbit and human eyes. A 1 M solution dropped on the normal rabbit eye caused pain and chemosis, and when dropped repeatedly on deepithelized eyes for 15 minutes caused marked swelling of the corneal stroma, intense conjunctival chemosis with small conjunctival hemorrhages, and hemorrhagic iritis. A 0.1 M solution dropped once on the normal human eye caused stinging similar to that produced by 0.5% tetracaine hydrochloride, but the discomfort was much more persistent. There was no damage evident. The same solution dropped continuously for 15 minutes on rabbit eyes which had had the corneal epithelium removed with a knife edge caused a little more corneal edema, chemosis, and hyperemia of the iris than did removal of epithelium alone; however, healing was complete in three days, as it

was in unexposed deepithelized controls. The exposed corneas were then as clear as the control corneas. A 0.01 M solution dropped on the normal human eye produced practically no discomfort, and repeated dropping for periods up to 15 minutes caused no damage, but only a mild pale edema of the conjunctiva. The same low concentration dropped continuously for 30 minutes on rabbit corneas which had been deepithelized by scraping or by means of butyl alcohol caused no disturbance other than mild pale conjunctival edema and mild edema of the corneal stroma, not significantly worse than that produced by deepithelization alone. The eyes returned to normal in two to four days. The same 0.01 M solution injected intracorneally (0.05 to 0.1 ml.) with a needle produced a pronounced bluish swelling of the cornea localized to the area injected, similar to that produced by injection of water or sodium chloride solution. The original discoloration took several days to clear and left a faint gray opacity, which disappeared in approximately two weeks. The amount of reaction was somewhat greater than is produced by intracorneal injection of 0.9% saline solution, from which the cornea clears in 24 to 48 hours. The same 0.01 M solution of EDTA injected into the anterior chamber caused a more diffuse corneal edema and marked hyperemia of the iris and conjunctiva. Clearing was somewhat slower than following the simple intracorneal injection. From these observations it was concluded that 0.01 M (approximately 0.4%) neutral solution of EDTA was sufficiently safe and nonirritating for dropping on the denuded human cornea for a period of 15 minutes, but not for injection into the eye. (It appeared also that 0.1 M solution might reasonably be tried on certain human eyes; however, for removal of calcific opacities it was found unnecessary to go to this higher concentration.)

Neutral sodium citrate, 5% (0.19 M) solution, and ammonium tartrate, 10% (0.54 M) solution, could be dropped continuously on the denuded rabbit cornea for 30 minutes without producing severe disturbance or permanent damage. In both cases there was mild stromal edema, which cleared in about a week, but in the case of the ammonium tartrate there was in addition rather intense hyperemia of the iris, which lasted two to three days. From these observations and from previous clinical experience, the impression was gained that, although both these solutions were reasonably safe to employ on the cornea, the ammonium tartrate solution, was undesirably irritating and painful.

"Calgon" applied to rabbit eyes caused hemorrhages from the conjunctival blood vessels at a rather low concentration. This effect was observed when the eye was bathed for 15 minutes with a 5% solution whether or not the corneal epithelium had been removed. It was accentuated when the epithelium was removed by means of butyl alcohol. The 5% solution had little effect on the cornea unless the epithelium was removed; then it produced moderate stromal turbidity and marked iritis, which lasted several days. A 0.1% solution of "calgon" applied for 15 minutes caused mild chemosis but no hemorrhages and practically no disturbance of the cornea whether the cornea was denuded or intact.

REPORT OF CASES

CASE 1.—In the only eye of a man aged 24 band keratopathy (from old chronic sympathetic ophthalmia) obscured the axial portion of the cornea. Vision was 20/200 with or without the pinhole disc or lenses. An initial treatment consisting of irrigation of the intact corneal surface with 0.01 M neutral EDTA for 15 minutes, with topical use of tetracaine for anesthesia, produced no evident change in the cornea. There was only slight conjunctival edema immediately

following treatment and no discomfort at any time. Two days later the procedure was repeated, but this time a small patch of epithelium was removed with a knife edge over the temporal end of the band. During the irrigation a little localized clearing was evident in 10 minutes, and in 15 minutes the cornea was essentially clear where the epithelium had been removed. There was very little reaction to the treatment and two days later the same procedure with removal of epithelium was carried out on the lower portion of the cornea, and, finally, in another two days, in the pupillary area. Each time the epithelium healed promptly, and there was very little conjunctival reaction. The final result was that the treated areas of the cornea were cleared, and a fair view of normal optic disk and retinal vessels could be obtained, despite old keratic precipitates and an inflammatory membrane on the lens. Vision, however, became no better than 20/70, presumably owing to disease of the posterior segment.

Case 2.—One eye of a man aged 58 had a superficial but subepithelial band of corneal opacity from a lime burn incurred 2½ months previously. This opacity resembled frosted or ground glass, appearing with the biomicroscope as a lacy pattern of fine white lines in the anterior stroma covered by clear epithelium. The pupillary area of the cornea was involved by the opacity, and vision was 20/100, improvable to 20/50 with a pinhole disc. Irrigation with 10% neutral ammonium tartrate solution, with topical use of tetracaine for anesthesia, was tried but had to be discontinued in five minutes because of severe burning discomfort, and nothing was accomplished. A trial irrigation of the eye with the epithelium intact was then carried out with 0.01 M neutral EDTA for 20 minutes, with local application of tetracaine for anesthesia. There was no discomfort, no reaction except mild transient conjunctival edema, and no clearing of the cornea. Finally, five days later, a patch of epithelium, approximately 2 mm. in diameter, was removed with a knife edge from the vertex of the cornea without disturbing the underlying opacity. Then 0.01 M neutral EDTA was dropped on continuously for a period of 10 minutes, during which the opacity in the deepithelized area disappeared and the stroma appeared normal with slit-lamp biomicroscopy. There was moderate discomfort for 24 hours, but the epithelium healed rapidly. Vision was 20/30—3 in four days, and subsequently 20/30. During three months of subsequent observation the pupillary portion of the cornea has continued to be clear and the adjacent, untreated, areas to be opaque.

Case 3.—In one eye of a woman aged 62 phthisis bulbi and band keratopathy were accompanied by discomfort of a scratchy nature, which was thought to be due to the extrusion of flakes of calcific material through the corneal epithelium. Dissolution of the calcific material was attempted first by means of 5% (0.19 M) sodium citrate solution dropped on the eye after a patch of epithelium had been removed with a knife edge. After 10 minutes of irrigation no change in the opacity was observable. Then an additional patch of epithelium was removed, and 0.05 M neutral EDTA (five times the usual concentration) was dropped on the cornea. After five minutes of irrigation with this solution some thinning of the band was apparent in both denuded patches, and this was fairly definite by 10 minutes. By 15 minutes the initial clearing was somewhat obscured by development of some gray stromal edema in the deepithelized areas. There was little conjunctival and no iritic reaction, but the patient had considerable discomfort during the next 12 hours. In two days the epithelium was healed, with only a few dense calcific particles remaining near the limbus where the epithelium had not been removed at the time of treatment. The patient's original discomfort was relieved. It was concluded from this case that 5% sodium citrate solution had little effect on calcific corneal opacities, and that 0.05 M neutral EDTA was effective and when dropped on the cornea for 15 minutes was not seriously injurious. However, it did appear that this solution caused more discomfort and corneal edema than the weaker, 0.01 M, solution, which was employed in the other cases.

Case 4.—A debilitated man aged 44 with Hodgkin's disease had a white band of calcific opacities in the lower portion of both corneas. Occasional scratchy, foreign-body sensations of brief duration had been present for several months, becoming more bothersome in the right eye in the two weeks preceding examination. The band keratopathy had a small rough area at 6 o'clock, where it seemed that some of the calcific material had been lost spontaneously. The right eye was treated by irrigation with 0.01 M EDTA for 15 minutes after application of 0.5% tetracaine hydrochloride for anesthesia. The epithelium was not removed. Little effect was apparent except for dissolution of a small amount of the opacity in the 6-o'clock rough area. There was no discomfort and no reaction except for slight pale edema of the conjunctiva.

Three days later the patient reported that he was free of the foreign-body sensation in the treated eye. It is assumed that the original discomfort was caused by particles which were extruding through the epithelium and that those particles which were partly exposed were dissolved by the irrigation with EDTA.

CASE 5.—A woman aged 66 had extensive band keratopathy in both eyes, from old chronic uveitis. With topical anesthesia, one eye was treated by removal of the epithelium from the central two-thirds of the cornea with a knife, the opacity being left undisturbed. The cornea was irrigated with 0.01 M neutral EDTA for approximately 20 minutes, the procedure being interrupted three or four times for application of another drop of tetracaine solution. The pattern of dense corneal opacities gradually faded and was replaced by diffuse grayish stromal edema. Moderate discomfort followed the procedure. The cornea healed promptly, and within two days it was possible to examine the iris, pupil, and lens. The lens, which was cataractous, was extracted uneventfully the next day, without any unusual reaction in the previously treated cornea.

CASE 6.—A man aged 30 accidentally splashed slaked-lime plaster into his right eye. After a 30- to 60-minute delay, the eye was irrigated with water. On his arrival at the hospital, 20 hours later, there was a diffuse gray, ground-glass type of opacity of the lower nasal third of the cornea, obscuring all view of the iris in this area. Biomicroscopy showed the opacity to consist of many tiny gray dots and fine lines in the anterior layers of the stroma. Epithelium was absent. The eye was irrigated for 15 minutes with neutral 0.01 M EDTA, and at the end of irrigation the opacity appeared to be entirely gone, by both gross inspection and biomicroscopy. The epithelium regenerated slowly during the following week, and the conjunctiva remained hyperemic somewhat longer, but at last examination, two months later, the eye was clinically completely normal except for fine optical irregularity in the anterior stroma, just discernible by biomicroscopy. Vision (uncorrected) was 20/30.

CONCLUSIONS

Calcific corneal opacities, such as result from lime burns or occur in the clinical entity of band keratopathy, may be dissolved by means of the neutral sodium salt of ethylenediamine tetraacetic acid (EDTA). If epithelium overlies the opacity, this epithelium must first be removed. The denuded area is then irrigated for 15 minutes with a sterile 0.01 M solution of EDTA.[3] These procedures are carried out with the use of topical anesthesia.

Removal of calcific deposits from the cornea may be indicated for improvement of vision or for relief of discomfort from particles which are extruding through the epithelium.

In the case of fresh-lime burns with a ground-glass type of corneal opacity, it is advantageous to apply the solution of EDTA before the epithelium grows over the opacity (i. e., within the first 24 hours), but this need not be regarded as an emergency procedure, provided that thorough irrigation and cleansing of the conjunctival sac with water or saline solution are carried out in the usual manner as soon as possible after the exposure to lime.[4]

243 Charles St.

Dr. David Cogan assisted in some of the clinical treatments, and Miss Elizabeth O. Cushing assisted in the experimental investigation.

3. This solution may be prepared from analytical-grade disodium ethylenediamine tetraacetate dihydrate (also called "disodium versenate"), obtainable from the Bersworth Chemical Co., Framingham, Mass. The solution is prepared by dissolving 0.37 gm. of this compound in 100 ml. of distilled water and adding 0.10 gm. of sodium bicarbonate. Sterilization is accomplished by autoclaving or boiling.

4. Grant, W. M.: Chemical Burns of the Eye: Emergency Treatment, M. Clin. North America **36**:1215, 1952.

RADIOACTIVE STRONTIUM THERAPY OF THE EYE

Corneal Biostandardization and Evaluation of an Applicator for Use in Ophthalmology

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BETA irradiation of the eye remains relatively unemployed because of inconvenience, practical difficulties, and, in some instances, potential radiation hazard to the operator or to the patient's lens, or occasionally to both; but, because this form of superficial radiation therapy is both safe and effective when used properly in the conditions for which it is indicated and since it has no therapeutic equivalent in some instances, the continuing search for an improved ophthalmic applicator has led to the use of artificially radioactive isotopes.

Radioactive strontium (Sr^{90}) was chosen for the source material by Friedell and his associates,[1] who were the first to use this fission product in an applicator for ophthalmic use. Following the lead of this laboratory model, commercial physicists recently developed a clinical model, the RA-1 Medical Applicator.[2]

The effects of clinical treatments with new applicators of this type are certain to be somewhat unpredictable at first, because the physical measurement of beta radiation and the calibration of beta radiation applicators are not yet fully dependable as a basis for calculation of the dose which will produce an expected effect.

It is the purpose of this study to evaluate the Sr^{90} applicator (RA-1) in terms of some of its experimental radiobiologic effects on the rabbit cornea, in an effort to place its clinical use on a more secure and effective basis.

MATERIAL AND METHOD

The Sr^{90} applicators (Fig. 1), Nos. 29 and 153,[3] used in this study had the following specifications[4]: The radioactive source material, said to be about 25 mc. of Sr^{90} in equilibrium,

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1. Friedell, H. L.; Thomas, C. I., and Krohmer, J. S.: Beta-Ray Application to the Eye, with Description of Applicator Utilizing SR^{90} and Its Clinical Use, Am. J. Ophth. **33**:525-533 (April) 1950.

2. Manufactured by Tracerlab, Boston.

3. Applicator 153 was made available for this study through the cooperation of Dr. L. L. Garner, Milwaukee.

4. Tracerlab, Inc.: Instruction Manual Pertaining to the Use of the RA-1 Medical Applicator, Serial No. 29, 1951.

a pure beta-radiation emitter with a half-life of 20 years, was spread uniformly at the contact surface. This surface was circular and had an active diameter of 7.8 mm. (area, 47.7 sq. mm.) and an actual diameter of 12.7 mm. The radioactive strontium (Sr^{90}) was hermetically sealed under the applicator face, which consisted of 2 mils (0.002 in.) of stainless steel and 10 mils (0.01 in.) of aluminum.

The calibrations for these instruments, as stated by the manufacturer, were 22.9 (No. 29) and 45 (No. 153) rep per second, respectively.

On a subsequent recalibration by the manufacturer, a little more than a year later, the dose rate of Applicator 29 was found to be 20 rep per second.

A clear plastic disc, 10 cm. in diameter and 6 mm. in thickness, was provided on the applicator handle as a shield for the hand.

Fig. 1.—The Sr^{90} (RA-1) applicator.

In the absence of a mechanical holding device, each applicator was held vertically in contact with the rabbit cornea by supporting the plastic disc with an ordinary ring stand; this provision was necessary during the long treatment times used in some of the experiments.

The decay scheme [5] of Sr^{90} is characterized by two beta spectra, a weaker one (maximum energy, 0.65 million electron volt [mev]; average, 0.195 mev) from Sr^{90}, which results in the formation of Y^{90}, and a more energetic one (maximum, 2.16 mev; average, 0.8 mev), which transforms Y^{90} into the stable end-product of this series, Zr^{90}.

The dose (depth dose) at a tissue depth of 4 mm. (lens level) is indicated to be about 6% of the surface dose, and it is less than 1% at a tissue depth of 6.5 mm. The half-value layer is approximately 1 mm. in unit-density material.

5. Friedell, Thomas, and Krohmer.[1] Tracerlab, Inc.[4]

Thirty-six rabbits, weighing between 4 and 6 lb. (1.8 and 2.7 kg.), usually pigmented, were used in the experiments. General anesthesia was obtained from intravenous administration of pentobarbital (nembutal®). Ocular fixation, for eyes receiving less than 30,000 rep, was obtained by two bridle sutures, but all other rabbit eyes were proptosed for fixation during the treatments. In spite of this arrangement, several treatments had to be considered void because of gross movement, nystagmus, or applicator creeping during the long exposure.

Forty-one rabbit eyes were considered accurately exposed to the Sr^{90} applicators. By use of different exposures in the two eyes of all animals treated bilaterally, it was possible to minimize the error introduced by the variations in individual response among rabbits, a factor which was found to be considerable in these, as well as in previous, beta-radiation experiments.

Treatment doses are expressed in rep (roentgens equivalent physical), based on the manufacturer's calibrations of the instruments.

Grading of the lesions (Table 1) was done in the same way as in previous, similar studies,[6] in which the method used was a modification of Hughes and Iliff's [7] procedure.

Twenty-nine rabbit corneas were exposed to various contact doses from Applicator 29 to determine the minimum inflammatory dose and to follow the graded course of the lesions produced by larger doses. The minimum inflammatory dose was then determined also for Applicator 153.

TABLE 1.—*Method of Grading Corneal Lesions**

Description	Maximum Score
Corneal lesions	
Opacity (density × area) 4 × 4 =	16
Edema	3
Ulceration (depth)	4
Vascularization (sq. mm. area/20)	7
Total (maximum response)	30

* Modified from the method of Hughes and Iliff.[7]

RESULTS

Determination of Minimum Inflammatory Dose.—The 12 eyes of six rabbits were treated with Applicator 29, using single contact applications of 1,000, 2,000, 3,000, 6,000, 9,000, 11,000, 15,000, 20,000, 25,000, 30,000, and 40,000 rep. Two rabbits died of intercurrent disease after 155 days of observation; the remaining four rabbits were observed for 200 days. Only in the eye exposed to 40,000 rep did a corneal lesion develop, which attained a peak grade of 7% of the maximum possible.

Two additional rabbit eyes were exposed to 30,000 rep each, and both failed to produce a gradable response, although both eyes presented a faint, ephemeral epithelial haze during the third postirradiation week.

It was subsequently found that 35,000 rep was required in a single contact dose to produce consistently an unequivocal minimum inflammatory response on the rabbit cornea. The mean corneal score for this minimum inflammatory dose group was approximately 3% of the maximum possible (Table 2).

The minimum inflammatory dose, determined by Applicator 153 by the same procedure, was found to be 35,000 rep also.

6. Wilson, F. M.: Beta Irradiation: Evaluation of Radium-D Applicator for Ophthalmic Use, Am. J. Ophth. **33**:539-548 (April) 1950.

7. Hughes, W. F., Jr., and Iliff, C. E.: Effects of Beta Irradiation on the Rabbit's Eye, Am. J. Roentgenol. **56**:502-512 (Oct.) 1946.

Our determinations of the minimum inflammatory dose for Applicators 29 and 153 and those of Kahn [8] for Applicator 18 were strikingly similar:

Applicator No.	M. I. D.* (Rep)
29	35,000
153	35,000
18	36,000 (Kahn [8])

* M. I. D. means minimum inflammatory dose.

Corneal Lesions Produced by Single Contact Doses Greater Than the Minimum Inflammatory Dose.—For this series, 21 eyes of 18 rabbits were divided into seven groups, which groups were exposed to various contact doses with Applicator 29 (Table 2). Doses ranged from 40,00 to 130,000 rep, and, except for two rabbits which died of intercurrent disease early in the experiment, all animals were under observation during periods varying from 90 to 410 days.

A dose of 70,000 rep (2 minimum inflammatory doses) resulted in lesions which averaged 42% of the maximum possible score. The severest lesion (66%)

TABLE 2.—*Rabbit Corneal Lesions Produced by Various Exposures to the Sr^{90} (RA-1) Applicator*

Dose						
Rep	Time	Approximate Gm.-Sec.	Approximate M. I. D.*	No. of Eyes	Average Mean of Maximum Lesion (%)	S. E.†
35,000	25' 40"	38	1	4	2.9	± 1.4
40,000	29 20	44	1.2	3	4.2	± 1.5
50,000	36 40	55	1.5	5	15.3	± 8.1
60,000	44	65	1.7	3	21.5	± 8.2
70,000	51 20	76	2.0	4	42.1	± 6.5
80,000	58 40	87	2.3	3	41.2	± 14.7
100,000	73 20	110	3.0	1	66.0	.....
130,000	95 20	143	3.7	1	63.0	.....

* M. I. D. means minimum inflammatory dose.
† S. E. = standard error of the mean.

resulted when the dose reached 100,00 rep, and the score was not significantly different when the dose was increased to 130,000 rep, probably because of the inaccuracy of application during these unusually long treatment times.

Ulceration (Table 3) occurred in a total of 13 eyes, and in 3 eyes after doses as low as 35,000, 40,000, and 50,000 rep, respectively; in all rabbit eyes in which ulceration occurred, the average exposure was 71,153 rep, or approximately 2 minimum inflammatory doses.

The ulcerations developed rather late generally and, on the average, were present from the 94th until the 178th day. The average residual condition of the rabbit cornea at the end of this period was poor, there being vascularization, heavy granulation tissue, scar formation, or, in some cases, distortions and facets following necrosis and thinning; several eyes were disorganized after perforation.

The earliest ulceration occurred on the 28th day after exposure to 80,000 rep, and the latest ulceration occurred on the 181st day after exposure to a dose of 40,000 rep.

8. Kahn, M.: Unpublished data from the University of Illinois College of Medicine; cited by Hughes, W. F. Jr.: Beta Radiation Therapy in Ophthalmology, to be published.

Perforation occurred in six eyes after doses ranging from 35,000 to 80,000 rep. The earliest perforation occurred on the 52d day, after a dose of 70,000 rep, and the latest, on the 244th day, after a dose of 35,000 rep.

Two eyes irradiated with 100,000 and 130,000 rep, respectively, ulcerated but did not perforate.

Graded Course of the Lesions Produced by Various Exposures.—The lesions of the rabbit corneas produced by the Sr^{90} applicator consisted of early, delayed, and late changes.

Early Effects: These appeared as corneal opacities, varying from a faint haze to a dense onyx color, and edema, ranging from epithelial bedewing to stromal hydration and large vesicle formation, the degree depending on the amount of radiation used and the intensity of response. Associated with these changes were varying degrees of conjunctivitis, blepharitis, and iritis.

TABLE 3.—*Ulcerations of Rabbit Corneas After Irradiation with Sr^{90} (RA-1) Applicator*

Rabbit Eye (No.)	Dose (Rep)	Interval During Ulceration (Days)	Ulcer Depth (Grade)	Final Condition
26 L	35,000	163-244	4 (perforation)	Phthisis
6 L	40,000	181-218	3	Rabbit died 218th day
19 L	40,000	50- 61	4 (perforation)	Phthisis
9 L	50,000	122-259	3	Healed, scarred
17 L	70,000	39-140	4 (perforation)	Panophthalmitis
24 L	70,000	58-117	3	Healed, scarred
25 R	70,000	52-111	4 (perforation)	Healed, scarred
11 R	80,000	28- 69	4 (perforation)	Panophthalmitis
21 R	80,000	168-318	4—	Died 318th day
22 R	80,000	170-240	4 (perforation)	Healed, scarred
28 L	80,000	105-178	2	Died 178th day
12 L	100,000	59-145	3	Healed, scarred
19 R	130,000	34-223	4—	Healed, scarred
Averages:	71,153	94-178	3+ (85%)	Severe residual effects

Delayed Changes: These consisted of corneal ulceration, perforation, vascularization, pannus formation, and, finally, healing, usually with a permanent scar.

Late Changes: These appeared as exacerbations or recurrences of the original inflammatory lesions, with or without necrosis, ulceration, or perforation.

Comment: Generally, after an initial delay, lasting from two to eight days, the lesions were characterized by a course of development which was moderately rapid during the first three weeks after irradiation (Fig. 2). After this time the lesions produced by doses of less than 60,000 rep began to subside, whereas the course of lesions following greater exposures progressed, but more slowly than before, from one to three months being required for maximum development.

Improvement was slow and gradual in all cases, being occasionally interrupted by aberrant effects or late exacerbations. These aberrant and late effects had little, if any, relationship to dosage (Table 5).

The most unusually severe, late exacerbations occurred in Eyes 6L and 26L, exposed to 40,000 and 35,000 rep, respectively. After irradiation, as usual, both eyes promptly exhibited relatively innocent lesions, which improved. By the 56th and 90th postirradiation days the corneas appeared clear and normal in all respects and remained so for about three months. However, on the 163d and 162d days,

respectively, the lesions reappeared. Both eyes then became worse; a Grade-3 corneal ulcer developed in eye 6L, and the cornea of Eye 26L perforated 81 days later (the 244th postirradiation day).

No lens changes attributable to the effects of radiation were observed grossly in any of the rabbit eyes used in this study.

Routine wipe tests performed at different times during the course of the study gave no evidence of applicator leakage.

CLINICAL OBSERVATIONS

After determination of the minimum inflammatory dose and establishment of definite trends of the lesions produced on rabbit corneas by these applicators, the use of the applicators was begun on human eyes which presented indications for beta irradiation. To date, the Sr^{90} applicators have been used only on previously untreated eyes, and often on rather heavily vascularized areas suitable for observation of radiation effects at various depths. So far, one or both eyes of 22 patients have been treated one or more times.

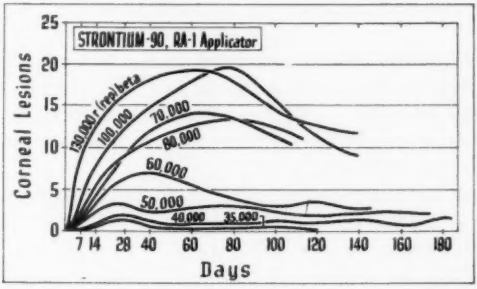

Fig. 2.—Graded course of the lesions (exclusive of late and aberrant effects) produced in rabbit corneas by beta irradiation with unfiltered Sr^{90} of various doses.

In some instances, particularly when the site of irradiation was in the area of the upper or the lower limbus rather than near the horizontal meridian, the applicator proved to be too large in diameter for use without considerable difficulty.

The first doses administered were smaller than doses subsequently found necessary. These lower dose levels, consisting of a few hundred reps, were completely without gross or biomicroscopic effect when the eyes were observed for as long as three months after the irradiation. The radiation delivered was gradually increased; with doses calculated in terms of calibration, it was found that 12,000 rep, if given in one contact dose with good ocular fixation and steady application, produced a mild, superficial effect equivalent to that usually obtained with 2 gm.-sec. of radon exposure with the Hughes applicator.[9] Appraised with the slit-lamp biomicroscope, the clinical effects from exposure to 14,000 rep appeared about equal to those following a 3-gm.-sec. radon exposure, and 16,000 rep usually produced a satisfactory clinical response in all areas except those of deep vascularization, although not infrequently this dose had to be repeated in given areas.

9. (*a*) Wilson.[6] (*b*) Hughes, W. F., Jr.: Beta Radiation Therapy in Ophthalmology, to be published.

DETERMINATION OF SKIN-ERYTHEMA DOSE

The Sr^{90} Applicator 29 was applied to the volar skin surface of the forearm of seven subjects. The doses were delivered by direct contact and varied in amount from 300 to 3,000 rep. Although tanning or mild erythema occurred two or more days after application of the lower doses, it was found that 2,500 rep (about 0.07 M. I. D., or 2.7 gm.-sec.) was required to produce a first-degree erythema within 24 hours.

COMMENT

The prolonged times found necessary for clinical treatment in these studies are consistent with the experimental finding of the relatively high minimum inflammatory dose (35,000 rep) for the rabbit cornea.

The fact that the minimum inflammatory dose was found to be 35,000 rep for both applicators used in this study, although their calibrations differed by a factor of nearly 2—this, together with the fact that Kahn,[8] using the same method for another Sr^{90} applicator (No. 18), independently obtained a similar result (36,000 rep)—indicates a certain uniformity in the manufacturer's method of physical calibration of these applicators, regardless of the absolute accuracy of the measurements obtained.

It is apparent that the effective surface-dose rate was much reduced from that which might be expected from the millicurie load of the applicator, and it seems likely that the principal factor in this loss of efficiency is increased filtration, due to the thickness of the metals at the applicator face, and perhaps only slightly to self-absorption within the applicator.

Regarding the dose rate, however, some confusing contradictions arise from the comparison of this applicator with the pilot model of Friedell and his associates.[1] Whereas Friedell's applicator, containing about 100 mc. of Sr^{90}, was said to have an output of 5.4 rep per second and was used in clinical doses of about 300 rep weekly for a total of about 1,200 rep, or a little more, the applicators used in this study contained about 25 mc. of Sr^{90}, but were calibrated at 22.9 and 45 rep per second; nevertheless these applicators require a much longer, not shorter, treatment time than that of the Friedell instrument. The explanation of these facts is not readily found.

In a previous study, it was shown that the relationship of the radiation effects on the rabbit cornea of two different source materials (radium D and radon) tended to be linear throughout various increments of dose, so that it is probably not inaccurate to compare different applicators on the basis of their carefully determined minimum inflammatory doses when the method of determination is constant.

It was also shown [6] that the minimum inflammatory dose for the rabbit cornea was 10 gm.-sec. for the Hughes radon applicator, in which self-absorption and filtration effects are minimal. This figure compared with the findings of the present study, therefore, in which the minimum inflammatory dose for the Sr^{90} applicators (RA-1) was 35,000 rep, or approximately 38 gm.-sec., indicates that radon has nearly four times the effectiveness of the Sr^{90} instrument.

In making this comparison, an equal millicurie load is assumed; actually, since the load of the radon applicator is usually more than this, its clinical effectiveness is increased proportionately. A comparison which also considers the active areas

of the two applicators is a measure of their relative absolute efficiency, an abstract number which has less meaning to the ophthalmologist than the relative clinical efficiency of the two instruments.

Clinically, the Sr^{90} applicators used in this study were frequently not easily placed in contact with human eyes except in areas near the horizontal meridian. This was due to two factors: the lack of a satisfactory mechanical device for making the long applications, and the excessive outside diameter (12.7 mm.) of the applicators, which made placement difficult in many cases and impossible in some.

In our opinion, a reduction of 3 or 4 mm. in the outside diameter and, at the same time, a change in the design to accommodate a mechanical holding device, perhaps one similar to that used for the radium-D plaque,[10] and/or an increase in the dose rate would greatly improve the practical usefulness of this applicator.

The lesions produced on rabbit corneas by various contact doses given with the Sr^{90} applicator followed a graded course somewhat similar to those from radon,[6] but with the following differences: The Sr^{90} lesions developed and regressed more slowly than those of radon; the incidence of ulceration was somewhat greater than

TABLE 4.—*Comparison of Ulcerations of Rabbit Cornea After Sr^{90} with Those of Previous Study*[6]

Applicator	No. Eyes Exposed to 1 M. I. D.* or More	No. Eyes Ulcerated	Average Ulcerating Dose (M. I. D.)	Average Ulcer Interval (Days)	Average Ulcer Depth
Radium D	26	6	2.6	10- 28	40%
Radon	24	8	2.8	28- 52	62%
Sr^{90}	24	13	2.0	94-178	85%

* M. I. D. is minimum inflammatory dose.

that following radon exposure and ulcerations were, on the average, deeper and later in appearance and disappearance (Table 4).

From a comparison (Table 4) of ulcerations, it appears that the stromal effects of Sr^{90} are certainly as deep as, and probably deeper than, those of radon. Two contributing factors are concerned in the increased depth dose of this applicator: the high energy of the beta particles from Sr^{90} and the amount of filtration in the applicator.

The lack of correlation between the dose and the development of aberrant effects (Table 5), such as perforation and late ulceration or lesion intensification, leads one to the suspicion of additional factors, perhaps three of which are individual variation, cage trauma, and infection.

It is notable that one rabbit received 130,000 rep to the right cornea (19 R) and 40,000 rep to the left cornea (19 L). The eye (19 L) receiving the smaller dose subsequently perforated, whereas the other eye (19 R) ulcerated but did not perforate. In this instance, individual variation seems to have had less influence than usual.

It is apparent that rabbit eyes should be observed for at least 200 days if the investigator wishes to include the late corneal changes in studies of this type.

10. Stevenson, W.: An Ophthalmic Applicator for Beta Radium-D, Mississippi Valley M. J. **70**:242 (Nov.) 1948.

Although the energy of beta particles from radium (or radon) reaches a greater maximum, the average energy of those from Sr^{90} (0.8 mev) is higher than the average energy from radium (radon) (0.65 mev). This is presumably because the proportion of longer-range electrons is higher in Sr^{90} and Y^{90} than it is in radium C. Moreover, in radium, but not in Sr^{90}, a number of atoms of the decay products disintegrate, with the release of some of their energy in the form of gamma radiation.

Lens damage due to beta rays was not observed grossly in this study, and beta-radiation cataract has not been reported previously; but Hughes,[9b] in a forthcoming article, reports two cases in which cataract developed about three years after beta-radiation doses of the order of 50 gm.-sec. administered over periods of about four months. Roughly, this total dose would amount to about 12 treatments of 16,000 rep each with the strontium applicator. In view of this report, although admittedly

TABLE 5.—*Aberrant Effects of Sr^{90} Beta Irradiation of Rabbit Cornea*

Lesion		Cornea	Days Post-irradiation	Dose (Rep)	Comment
Late intensification of opacity..		6 L	162	40,000	Progressed to deep ulceration (3+)
		26 L	163	35,000	Perforated 81 days later
		28 L	167	80,000	Mild exacerbation
		21 L	168	70,000	Deep ulcer developed concurrently
		22 R	184	80,000	Perforated 38 days later
		9 L	...	50,000	Gradually progressed for 185 days
Late ulceration		28 L	105	80,000	Still progressing on 178th day
		26 L	163	35,000	Perforated 81 days later (244th day)
		21 L	168	70,000	Large 4— ulcer (at 318+ days)
		22 R	170	80,000	Perforated 42 days later
		6 L	181	40,000	Grade 3 ulcer, progressing, at 218 days
		9 L	122 186 (recurrent)	50,000	Healed by 273d day; still healed on 427th day
Perforation.....	Delayed	25 R	52	70,000	Healed 39 days later
		19 L	61	40,000	Rabbit died 31 days later; healing cornea; phthisis
		11 R	69	80,000	Panophthalmitis
	Late	17 L	140	70,000	Panophthalmitis
		22 R	212	80,000	Healed 41 days later
		26 L	244	35,000	Healed 42 days later; phthisis

circumstantial, the slightly more energetic electrons of Sr-Y^{t} must also be considered potentially cataractogenic.

The face of the Tracerlab Sr^{90} applicator consists of 2 mils of stainless steel and 10 mils of aluminum. This amounts to a total filtration depth of 0.3 mm., considerably more than that in the Hughes radon applicator, in which the only filtration is due to the glass capillary tubes and about 1 mm. of air. The filtration is also more than is used in other, solid element applicators of similar nature, (radium-D applicator, 0.05 mm. aluminum; Iliff radium applicator, 0.1 mm. monel® metal). In addition to this filtration at the active face, the factor of self-absorption within the applicator is not entirely assessable, but is probably, because of the high specific activity of Sr^{90}, of much less importance than filtration in eliminating some of the short-range electrons, thus increasing the percentage of more energetic particles and the depth dose.

The skin-erythema dose, although determined for this applicator on human skin, had, in our hands, little to recommend it as a standardizing procedure in the prob-

lem of beta irradiation of the eye. This was due chiefly to three factors: the poorly defined end-point, the high incidence of individual variation, and the unreliability of a quantitative relation between the erythema response of human skin and clinical doses for the eye.

Since Sr^{90} is a pure beta-radiation emitter, this applicator has the advantage of being free of unwanted, penetrating gamma rays, greatly reducing the inconvenience of handling and minimizing some of the potential hazards of use which may be found in some other types of applicators.[11] As in the radium-D applicator, however, there is a small quantity of photon activity which is attributable to *Bremsstrahlung*, secondary x-rays formed by the transformation of energy from electron collisions with the surrounding materials of the applicator. This small amount of radiation can be disregarded clinically.

Availability, relatively low cost (about $300), and a half-life measured in years are additional advantages of the Sr^{90} applicator.

CONCLUSIONS

Two radioactive strontium (Sr^{90}) medical applicators (RA-1, Nos. 29 and 153) were evaluated by animal experiments and clinical trial.

The minimum inflammatory dose for the rabbit cornea was found to be 35,000 rep [12] for both applicators.

The average clinical dose for the human eye was about 16,000 rep,[12] delivered by single contact.

The advantages were relative permanency, availability, low cost, beta-ray emission without significant gamma radiation, and beta particles of adequate energy.

The disadvantages are prolonged clinical treatment time, a fault which is intensified by the lack of a suitable mechanical holding device; presumably an increased tendency to ulceration and to delayed reactions, as may be inferred from the animal experiments; difficulty of application in certain areas, due to excessive diameter of the instrument, and, at present, unreliability of the physical calibration of applicators as a basis for the calculation of the clinical dose.

Sr^{90} has certain highly desirable features and promise as a source material for use in ophthalmology, but, because of disadvantages of the applicator in its present form, it seems advisable to remodel the instrument, especially to improve the design and the dose rate, in order to increase its suitability for beta irradiation of the eye.

11. Wilson, F. M.: Applicators for Beta Irradiation of the Eye, Am. J. Ophth. **35**:645-656 (May) 1952.

12. These values are for the applicators used in this study only, and do not necessarily apply to other, similar applicators.

BELL'S PALSY SUCCESSFULLY TREATED WITH CORTISONE

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IN OCTOBER, 1951, Rothendler [1] reported satisfactory results in a case of Bell's palsy following the intramuscular administration of cortisone. The present report is that of a case of Bell's palsy in which cortisone, given orally, proved to be effective, even though it was first administered nine days after onset of the paralysis.

REPORT OF A CASE

L. W., a 45-year-old white woman, awoke on March 16, 1952, with paralysis of the right side of her face. When she was first seen, eight days later, her physical status was as follows: There was total lower-motor-neurone paralysis of the right side of her face. She was unable to wrinkle the right half of her forehead; she was unable to frown; when she was asked to close her eyes, the left eye closed, and the right remained open; there was eversion of the lower lid, and the eyebrow could not be elevated. The right eye was tearing, and the sclera was injected. The muscles of the right side of the face were immobile. The right half of the mouth was drooping. Voluntary movements, such as showing the teeth and attempting to whistle, were possible only on the left side and greatly increased the facial asymmetry. Posterior auricular pain was present. There was loss of taste in the anterior two-thirds of the tongue. There was no difficulty in swallowing. The structures of the neck were normal. No enlarged glands were found. Physical examination of the chest, abdomen, and extremities revealed a normal condition. The blood pressure was 124/84; the weight was 156½ lb. (71 kg.).

Oral treatment with cortisone (cortone® acetate) was started on March 25, nine days after the onset of the paralysis. She was given a total of 500 mg. during the first 24 hours, in five divided doses. At the end of the first day of treatment a dramatic improvement was noted. The posterior auricular pain had disappeared completely. Taste sensation was described as metallic, suggesting a return of function. Her right eye had stopped tearing, and the sclera appeared clear. Further pertinent data and dosage schedules are presented in the Table. At the end of the second day her taste returned completely to normal. By the fifth day she could close her right eye except for a small aperture, through which the sclera could barely be seen. The patient remarked that it no longer was an effort to close her eye. On the next day she could close her eye completely. By the eighth day movements of the muscles of the forehead, the right lower lid, and right side of the face were apparent. The drooping of the right side of the mouth was diminished, and she was able to separate the lips so that the teeth in this area were discernible. On the 10th day wrinkling of the right side of the forehead returned. She was able to elevate her right eyebrow; she could smile, and when she was asked to show her teeth, the right side of her mouth was nearly normal in appearance. During this 10-day period she gained

1. Rothendler, H. H.: Bell's Palsy Treated with Cortisone, J. Nerv. & Ment. Dis. **114**:346 (Oct.) 1951.

5½ lb. (2.5 kg.) in weight. The blood pressure showed no change. When seen on the 14th day, the patient stated that she had discontinued the medication at the end of the 12th day at her own volition, maintaining that she was cured and did not wish any further medication. No apparent effects followed this sudden cessation of therapy. At this time she could frown and wrinkle her forehead in a normal manner. She could close her right eye completely and could smile. The two sides of her face were similar. Her mouth was normal in contour, and her teeth showed equally on the two sides.

COMMENT

During the nine days after the onset of paralysis, and prior to the institution of cortisone therapy, there was no evidence of any return of nerve function. Within 24 hours after the institution of treatment an effect was evident. The progressive

Clinical Data and Dosage Schedule in a Case of Bell's Palsy Treated with Cortisone

Date	Dose of Cortisone, Mg.	Blood Pressure	Weight, Lb.	Comment
3/25	500	124/84	156½	.....
3/26	400	140/80	158	Loss of pain; reappearance of taste sense; cessation of lacrimation
3/27	300	136/80	158½	Taste normal
3/28	300	134/80	157¼	.....
3/29	300	.....	.....	.....
3/30	250	140/80	159½	Right eye closes; sclera barely visible
3/31	200	140/80	159½	Right eye closes
4/ 1	200	.....	.....	.....
4/ 2	200	128/76	159¾	Slight movement of muscles of face, forehead, lower lid, and mouth
4/ 3	200	.....	.....	.....
4/ 4	200	136/80	162	Right angle of mouth straightening; right eyebrow moves; mild wrinkling of forehead
4/ 5	150	.....	.....	.....
4/ 6	150	.....	.....	.....
4/ 7	None	.....	.....	.....
4/ 8	None	130/80	159¾	Forehead wrinkles; muscles of face normal

improvement and the return to normal within 12 days after the onset of treatment strongly suggest that the corticosteroid was the activating factor in the recovery process. The exact mechanism of action must at present be theoretical. Rothendler believes that the beneficial action may be due to the rapid reduction in the congestion of the nerve sheath in the bony canal relieving pressure on the involved nerve fibers.

Whether similar results may be obtained with smaller oral doses of cortisone can only be ascertained when more cases are available for study. The interesting feature in this case was that a result was obtained after the paralysis had been present for nine days.

CONCLUSION

A case of Bell's palsy is presented in which cortisone was given orally nine days after the onset of the paralysis. The striking improvement, commencing within 24 hours and continuing through a 12-day course of therapy, strongly suggests that cortisone is an effective agent in the treatment of Bell's palsy.

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INCIDENCE OF RETROLENTAL FIBROPLASIA IN A NEW YORK NURSERY

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SOURCE OF MATERIAL

A TWO-YEAR study of the incidence of retrolental fibroplasia was conducted in the premature nursery of the Babies Hospital. The ocular fundi of every surviving prematurely born infant who was admitted to the nursery were examined ophthalmoscopically at least once every week.

From Dec. 15, 1949, to Dec. 15, 1951, 437 infants were admitted to the nursery. One hundred forty infants died within seven days of admission. Seventeen infants died between 7 and 84 days after admission, and 5 of these 17 infants had retrolental fibroplasia which was recognized clinically before their death. Two hundred eighty infants were discharged from the nursery alive. In 75 of these children who lived retrolental fibroplasia developed, of whom 19 were left with serious involvement of one or both eyes.

All infants born in Sloane Hospital (obstetrical unit of Columbia-Presbyterian Medical Center) weighing 2,000 gm. or less at birth (189 babies) were transferred immediately to the premature infant nursery in Babies Hospital. The Premature Transport Service of the City of New York (operated by the New York City Departments of Health and Hospitals [1]) transferred 248 infants born in other New York Hospitals to the same premature nursery. The frequency distribution of these two groups of infants with respect to birth weight shows them to be dissimilar (Chart 1).

This work has been supported by a grant from the Dunlevy Milbank Foundation, Inc.

From the Department of Pediatrics and the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, the Babies Hospital, and the Institute of Ophthalmology of the Presbyterian Hospital.

1. Wallace, H. M.; Losty, M. A., and Baumgartner, L.: Report of Two Years' Experience in Transportation of Premature Infants in New York City, Pediatrics **9**:439, 1952.

The premature infants who came to the nursery via the Transport Service were selected in two known ways. 1. As can be seen in the frequency polygon, a larger proportion of these infants were of very low birth weight. 2. In most instances transfer took place after the first few hours of life, and occasionally as late as one week after birth. Selection in the Premature Transport Service group served to eliminate the infants who died shortly after birth, before transfer could be effected. Despite these glaring sampling dissimilarities of the two populations of infants, when due allowance was made for differences in birth weight by categorization in 100-gm. classes no significant difference in mortality was observed.

The distribution of the birth weights for 1950 as compared with those for 1951 of the infants in each of the two groups who survived was very similar below 1,700 gm. In both groups, the Sloane and the Premature Transport Service group, larger numbers of infants whose birth weights were above 1,700 gm., were admitted in 1950 than in 1951.

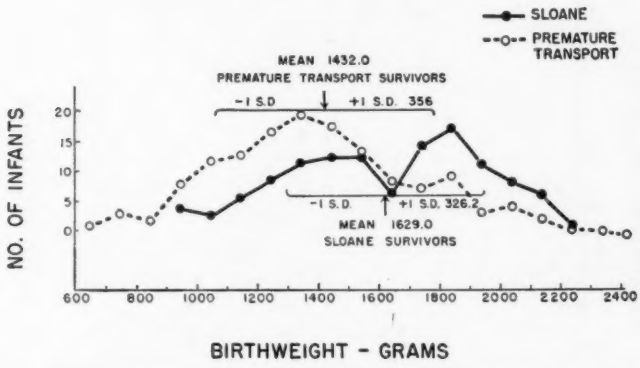

Chart 1.—Frequency distribution of total number of infants discharged from the premature nursery alive, compared as to place of birth: "Sloane Hospital"—the affiliated obstetrical service—and Premature Transport Service—those born in other New York hospitals and transferred to the nursery. The distributions of the two groups are dissimilar.

The incidence of retrolental fibroplasia in each 100-gm. birth-weight class was the same in the two groups (Sloane and Premature Transport Service).

A similar study was undertaken in the premature nursery of the Lincoln Hospital. The population of this nursery consisted of premature infants born in Lincoln Hospital and of infants transferred by the Premature Transport Service. Unfortunately, it was not possible to analyze the data obtained in this nursery in the same detailed manner as was possible in Babies Hospital. This experience, however, will be noted in Tables 1 and 2, which give the total incidence of the disease.

GENERAL STATUS OF INFANTS IN BABIES HOSPITAL BEFORE APPEARANCE OF RETROLENTAL FIBROPLASIA

Capillary hemangiomata which were raised and bright red were present at birth or developed later in 43 of the 280 surviving infants. In 20 of these infants retrolental fibroplasia developed, and 23 escaped the disease. All these cutaneous lesions

increased in size for a time and ultimately disappeared. The incidence of hemangiomata was inversely related to birth weight, and the general form of this incidence curve was lower, but similar to that of the incidence of retrolental fibroplasia (Chart 2). Of 116 infants whose birth weight was below 1,400 gm., 27 had hemangiomata, and in 15 of these infants retrolental fibroplasia developed. Eighty-nine did not have hemangiomata; in 47 of these retrolental fibroplasia developed. Thus, the incidence of retrolental fibroplasia was not significantly different among those infants who did and those who did not have hemangiomata. Nor was the time of appearance of the postnatally developing hemangiomata correlated with the time of appearance of the first ocular signs of retrolental fibroplasia.

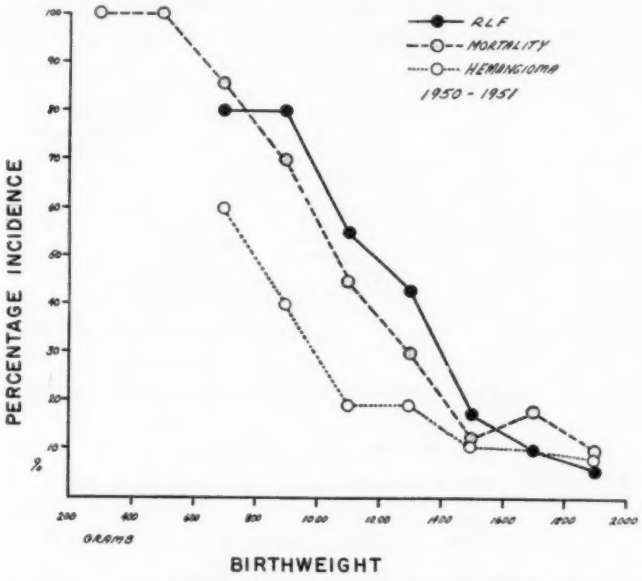

Chart 2.—Two-year (1950-1951) incidence of cutaneous hemangiomata and retrolental fibroplasia compared with mortality by 200-gm. (birth weight) classes. These three phenomena—cutaneous hemangiomata, retrolental fibroplasia, and mortality—are similar in that they are all inversely related to birth weight.

The condition of the 80 infants in whom retrolental fibroplasia developed, before the first signs of disease in the ocular fundus, was in no recognizable way different from that of infants who escaped. One infant had a cleft palate and harelip. No other congenital anomalies were noted.

One infant had an exfoliative dermatitis that was classified as Ritter's disease. Except for minor instances of superficial pyoderma, no other types of pyogenic infection were recognized before the clinical onset of ocular disease. A total of 55 of the 80 infants received antibacterial therapy before the onset of retrolental fibroplasia (penicillin, 42; chloramphenicol [chloromycetin®], 25; terramycin, 5; sulfadiazine, 2; aureomycin, 2, and sulfisoxazole [gantrisin®], 1).

Transfusions of either blood or plasma or both were administered to 18 of the infants before the onset of ocular disease. Medicinal iron was given to 12 of the affected infants.

All the infants received artificial formulae; 46 received only a half-skim-milk formula (alacta®) prior to the onset; 25 received only an evaporated-milk formula; 9 received a half-skim-milk formula followed by an evaporated-milk formula and were taking the latter ration at the time of discovery of the first signs of retrolental fibroplasia. The half-skim-milk formula contained 2.7 mEq. of sodium per 100 cc.; the evaporated-milk formula, 1.5 mEq. per 100 cc.

All the 80 infants were initially placed in incubators and given oxygen for periods varying from 3 to 63 days. The criteria for discontinuing oxygen administration were entirely extraocular and were applied on the basis of clinical judgment. Eleven

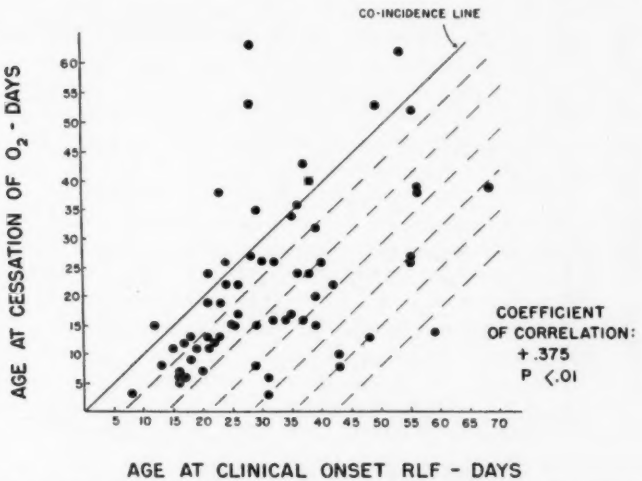

Chart 3.—Relation of the age at which oxygen administration was discontinued to the age at which the clinical onset of ocular disease was noted. The coincidence (unbroken) line plots the coincidence of these two events. The parallel (broken) lines divide off successive one-week intervals by which the onset of retrolental fibroplasia followed cessation of oxygen administration.

infants had been receiving continuous oxygen administration at the time of discovery of retrolental fibroplasia, and, as can be seen (Chart 3), there was no tendency for the disease to appear immediately after the cessation of oxygen administration. In 15 instances one to seven days elapsed between cessation of oxygen administration and the onset of retrolental fibroplasia; in 17 cases 8 to 14 days; in 13 cases 15 to 21 days, and in 13 cases more than 3 weeks. It was not startling to find (Chart 4) that the small infants were given oxygen for long periods and the large infants for shorter periods. However, it was unexpected that the disease had its onset late in small infants and early in large infants (Chart 8). The significance of the relationship noted between the age at clinical onset of disease and the age at cessation of oxygen

administration (Chart 3) may be due, in part, to a common relationship to birth weight (Charts 4 and 8). When the effect of birth weight is eliminated by the partial-correlation technique, the resulting correlation is not significant.[2] However, the association between the age at onset of disease and the birth weight (Chart 8) is not appreciably altered when the effect of the duration of oxygen administration is removed.[3] It was, therefore, not possible to conclude, as others have,[4] that a causal relationship existed between the cessation of oxygen administration and the onset of retrolental fibroplasia.

In contrast, as will be shown below, the severity of the end-stage lesion of retrolental fibroplasia was not related to birth weight or to the amount of oxygen administered.

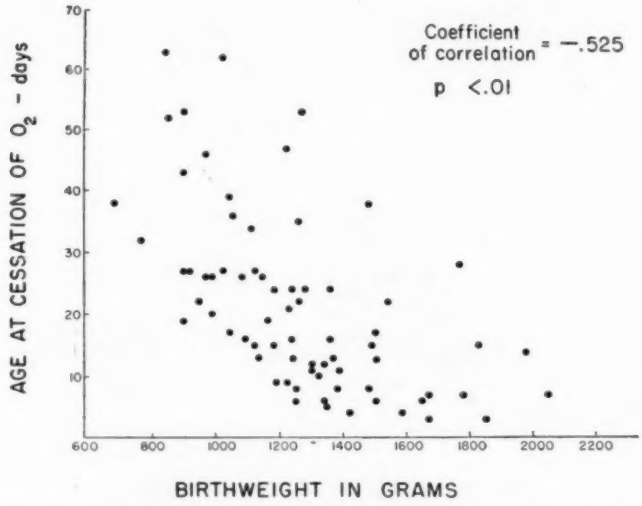

Chart 4.—Inverse correlation of the age, in days, at which continuous oxygen administration was discontinued and birth weight.

The medical management of the premature infants remained the same during the two years of the study. No change in policy concerning the administration of oxygen, the amount of sodium in the diet, or any other detail in the care of the infants separated 1950 from 1951.

2. Coefficient of partial correlation (age cessation oxygen: age onset retrolental fibroplasia, elimination of the variable, birth weight) $r_{12.3} = 0.14$ $p > 0.10$.

3. Coefficient of partial correlation (age onset retrolental fibroplasia: birth weight, with elimination of the variable, age of cessation of oxygen) $r_{1.23} = -0.40$ $p < 0.01$.

4. Szewczyk, T. S.: Retrolental Fibroplasia: Etiology and Prophylaxis: A Preliminary Report, Am. J. Ophth. **34**:1649, 1951; Retrolental Fibroplasia: Etiology and Prophylaxis, ibid. **35**:301, 1952. Ryan, H.: Retrolental Fibroplasia: A Clinicopathologic Study, ibid. **35**:329, 1952.

OPHTHALMOSCOPIC EXAMINATION OF PREMATURE BABIES

It was found advisable to examine all babies at least once a week. When examinations are done less frequently, the date of onset of the disease cannot be determined accurately.

Good dilation of the pupils is absolutely necessary for a satisfactory examination of the fundi. One drop of a 2% homatropine hydrobromide solution and 1 drop of a 10% phenylephrine (neo-synephrine®) hydrochloride suspension were instilled into each eye. Harmful effects from homatropine were not seen in this series. The phenylephrine occasionally caused blanching of the conjunctiva and lids in very small babies. The dilatation of the pupils was adequate after an hour even if the iris was heavily pigmented. Only in a very few affected children was dilatation unsatisfactory after these mydriatics.

For the examination itself, the baby was taken out of the incubator, put on a table, and immobilized. This was easily achieved by wrapping the child in a blanket. Ophthalmoscopic examination was possible with the infant in an incubator (isolette®) but was done thus only when the condition of the baby was precarious. The examiner stood at the baby's head and opened the lids with his fingers or instructed a nurse to pull down the lower lid as he raised the upper lid. The nurse stood at the infant's feet and gripped the head firmly. In this way a satisfactory examination was made in the large majority of smaller infants. Only larger or restless babies needed to be pacified with a moistened, sterile sugar ball.

The ophthalmoscopic examination should not be confined to the posterior segment, but should include the periphery, where the first changes may appear. It was usually possible to rotate the child's eyes in any desired direction by exerting gentle pressure of the fingers holding the lids.

While a weekly ophthalmoscopic examination is sufficient for the routine in a premature nursery, it was found necessary to examine affected infants or babies suspected of having the disease twice a week. Only thus were various progressions and regressions in the course of the disease appreciated.

Formerly all babies were examined up to the age of 4 months. At present, infants with normal fundi are not followed after the age of 3 months, since the onset of retrolental fibroplasia was never noted to occur after that time. When the patient was discharged before that age, ophthalmoscopic examinations were made every two weeks in a follow-up clinic, the same technique being employed.

The sugar ball is generally effective in placating the baby up to about the age of 4 months, after which he is less tolerant, and it becomes necessary to use a general anesthetic in indicated cases.

INCIDENCE OF RETROLENTAL FIBROPLASIA

Of the 80 affected infants observed in the Babies Hospital, 39 were males and 41 females.

Table 1 shows the total incidence of retrolental fibroplasia during 1950 and 1951 (Lincoln Hospital figures are included in this table). The criteria for the diagnosis were significant and progressive dilatation and tortuosity of the retinal vessels, with or without edema in the periphery of the fundus, hemorrhages, or neovascularization. As had been postulated, the incidence was inversely related to the birth weight. However, the relationship was not a perfectly linear one (Chart 2).

The incidence of retrolental fibroplasia increased during the second year of the study. Retrolental fibroplasia developed in 24 of 230 infants who were born during 1950 and in 56 of 207 infants born in 1951.

The incidence of retrolental fibroplasia was inversely related to birth weight, gestational age, and to a combination of these measures of the degree of prematurity. The change in incidence could not be explained on the basis of a change in the character of the populations with respect to the birth weights of the premature infants during the two years under comparison. There was a significant difference between the means of the birth weights of the total number of survivors in the two years.[5] However, 70 infants with retrolental fibroplasia were found among 184 infants whose birth weight was less than 1,700 gm. (20 infants with retrolental fibroplasia among 87 survivors in 1950; 50 infants among 97 survivors in 1951). The difference between the means of the birth weights of this segment of the population was insignificant (Chart 5). Also, as judged by the χ^2 test, the distributions, in 100-gm. (birth weight) classes, of the two populations of survivors weighing less than 1,700 gm. were similar.[6]

TABLE 1.—*Total Incidence of Retrolental Fibroplasia*

	Babies Hospital				Lincoln Hospital			
	1950		1951		1950		1951	
Birth Weight, Grams	No.	%	No.	%	No.	%	No.	%
Up to 1,000	5 (9)*	55	11 (12)	92	.....	..	3 (4)	75
1,001-1,250	10 (27)	37	16 (27)	59	2 (9)	21	6 (8)	75
1,251-1,500	5 (28)	18	18 (42)	41	5 (19)	31	14 (20)	70
1,501-1,750	0 (26)	0	5 (24)	21	1 (16)	6	12 (30)	40
1,751-2,000	3 (42)	7	1 (16)	6	0 (5)	0	0 (10)	0
2,001-2,250	0 (20)	0	1 (4)	25	Not examined		Not examined	
2,251-2,500	0 (2)	0	0 (1)	0	Not examined		Not examined	

* The figure in parentheses is the number of surviving babies with adequate follow-up study in this birth-weight group.

It was possible to calculate the gestational age in weeks, from the date of onset of the mother's last menstrual period, for 299 of the 437 infants in this study. Of these infants, 205 survived and were discharged from the nursery alive (98 in 1950; 107 in 1951). There was no significant difference between the means of the gestational ages of the survivors in the two years,[7] nor were the distributions of surviving infants in one-week (gestational age) class intervals different in the two years.

One hundred fifty-two surviving premature infants whose birth weight was less than 1,700 gm. did not differ in the two years with respect to the characteristic of a combination of birth weight and gestational age; that is, when these surviving infants were grouped into a double-frequency distribution in the form of a correlation table (Chart 6), the distributions of infants in each cell of the table were similar for the two years.[8]

5. Mean birth weight (155 survivors) 1950 = 1,591.7 ± 366.9 gm.; mean birth weight (125 survivors) 1951 = 1,423.8 ± 316.5 gm.; standard error of difference = 40.3 gm.

6. $\chi^2 = 6.29$; 10 degrees of freedom; $p > 0.70$.

7. Mean gestational age (98 survivors) 1950 = 32.2 ± 3.6 weeks; mean gestational age (107 survivors) 1951 = 32.0 ± 3.5 weeks.

8. $\chi^2 = 27.92$; 30 degrees of freedom; $p > 0.50$.

Two other observed phenomena indicated that there was no change in the populations of the two years under comparison: 1. There was no significant difference in mortality between 1950 and 1951 when the rates for 100-gm. birth-weight classes and birth weight-gestational age categories were compared by the chi-square (χ^2) test. 2. Similar numbers of hemangiomata were observed in the two years (21 in 1950; 22 in 1951).

The incidence of retrolental fibroplasia was significantly larger in 1951, after due allowance had been made for differences in distribution of birth weight, gestational age, or of the two simultaneously.[9]

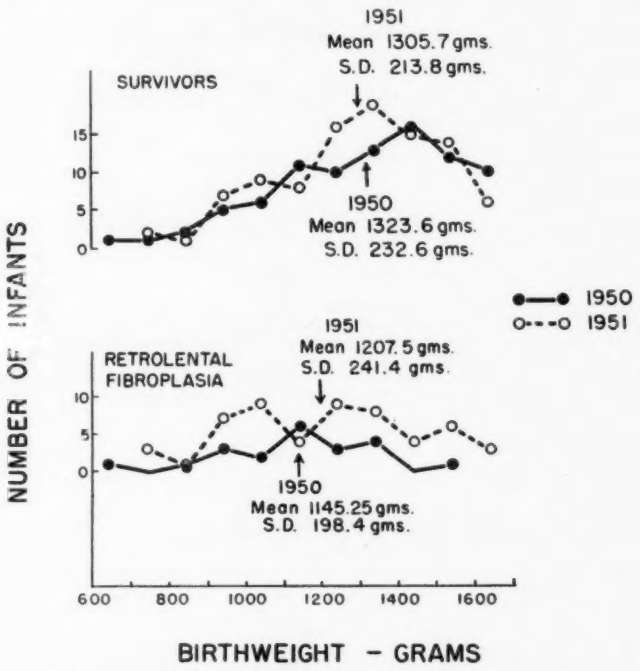

Chart 5.—Frequency distribution of the infants whose birth weight was below 1,700 gm. who were discharged from the nursery alive in 1950 as compared with similar values for 1951. Frequency distribution of the infants in this segment of the population in whom retrolental fibroplasia developed in each of the two years. The increased incidence in 1951 could not be explained on the basis of a change in the birth weight of the survivors below 1,700 gm.

The incidence of different degrees of end-stage involvement indicated that the severity of the disease bore no relation to birth weight (Table 2 and Chart 7) or to a combination of birth weight and gestational age. The increase which took place in

9. Cumulative χ^2 (incidence by 100-gm. birth weight classes) $= 7.2$; $p < 0.01$. Cumulative χ^2 (incidence by one-week gestational-age classes) $= 11.5$; $p < 0.01$. Cumulative χ^2 (incidence by cells in the birth weight-gestational age correlation table) $= 7.5$; $p < 0.01$.

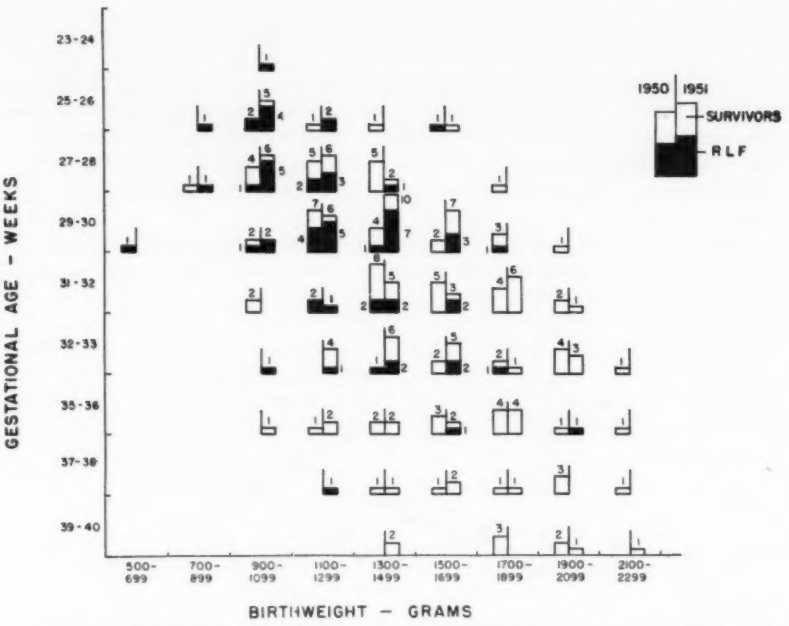

Chart 6.—Correlation table of birth weight with gestational age. In each cell of the table the number of survivors, of the given birth-weight (200-gm.) class and gestational-age (two-week) class, are grouped by year and the occurrence of retrolental fibroplasia. The incidence was greater in infants of both low birth weight and low gestational age. The increased incidence in 1951 could not be explained on the basis of a change in the distribution of the infants with respect to the relation of birth weight to gestational age.

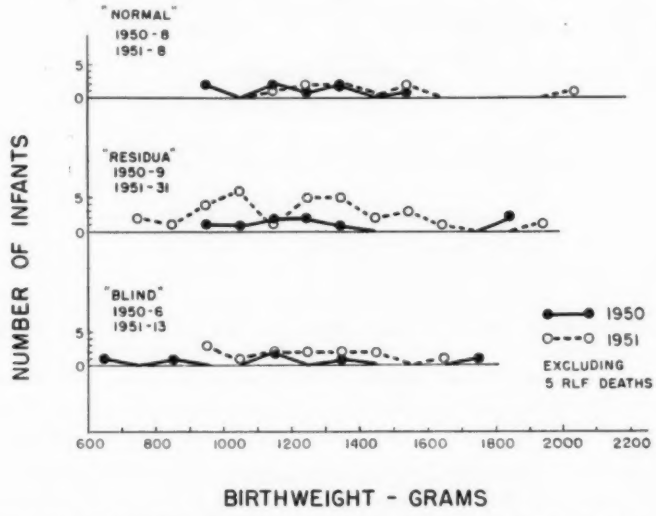

Chart 7.—The end-stage of retrolental fibroplasia with respect to birth weight for 1950 and 1951. "Blind" infants are those who had either complete or major retinal detachments in one or both eyes. Infants classified as having "residua" had cicatricial lesions in one or both eyes which were less severe but remained visible on late follow-up examination, usually with use of anesthesia. "Normal" infants are those who had no detectable cicatrix remaining in the retina.

TABLE 2.—*Infants with Retrolental Fibroplasia Progressing to Cicatricial Stage III or Worse, Ending with Permanent Visual Impairment in at Least One Eye*

	Babies Hospital				Lincoln Hospital					
	1950		1951		1950		1951		Total	
Birth Weight, Grams	No.	%	No.	%	No.	%	No.	%	No.	%
Up to 1,000	2 (5)	40	3 (11)	27	.....	..	1 (3)	33	6 (19)	31
1,001-1,250	2 (10)	20	4 (16)	25	2 (2)	100	1 (6)	16	9 (34)	27
1,251-1,500	1 (5)	20	5 (18)	28	2 (5)	40	3 (14)	21	11 (42)	26
1,501-1,750	0 (0)	0	0 (5)	0	1 (1)	100	3 (12)	25	4 (18)	22
1,751-2,000	1 (3)	33	0 (1)	0	0 (0)	0	0 (0)	0	1 (4)	25
2,001-2,250	.....	..	0 (1)	0	Not examined		Not examined		0 (1)	0
2,251-2,500	.....	..	.....	..	Not examined		Not examined		.....	..

* The figure in parentheses gives the total number of surviving infants with retrolental fibroplasia in this birth-weight group.

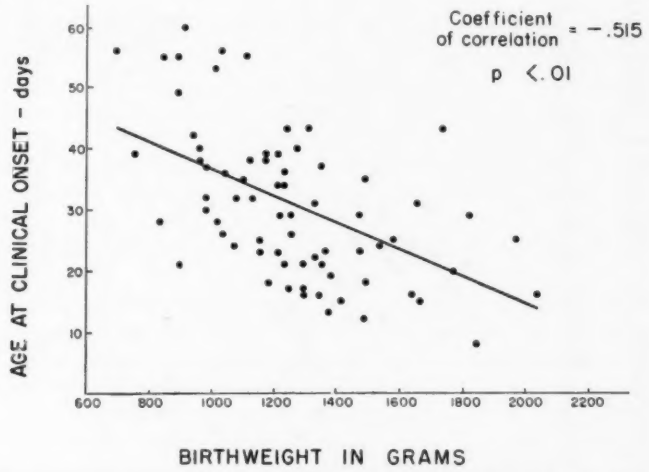

Chart 8.—Inverse correlation of clinical onset of retrolental fibroplasia to birth weight. The regression line has the following formula: age at onset (days) = 58.8 — 0.22 × birth weight (Grams).

1951 resulted in greater numbers of infants with blindness in at least one eye (6 in 1950; 13 in 1951) and a greater number of infants with detectable cicatricial residua in one or both eyes (9 in 1950; 31 in 1951). However, the number of infants whose fundi returned completely to normal was the same in the two years (8 in 1950; 8 in 1951).

RELATION BETWEEN BIRTH WEIGHT AND AGE AT WHICH FUNDUS CHANGES APPEARED

In 76 infants the day of onset was determined by weekly ophthalmoscopic examination. An inverse relationship was shown (Chart 8) between the birth weight and the age at which the first vascular signs of retrolental fibroplasia were noted. On the other hand, a similar relationship between the age of clinical onset and the

gestational age could not be established. It can be seen, however, that, with a single exception, the disease manifested itself before the expected day of birth at full term (Chart 9).

The infant found with disease at the earliest age (8 days) had received percomorph liver oil and ascorbic acid for two days and a standard evaporated-milk formula for six days. She received oxygen in a probable concentration of 40% for one day and of 30% for two more days, and then none.

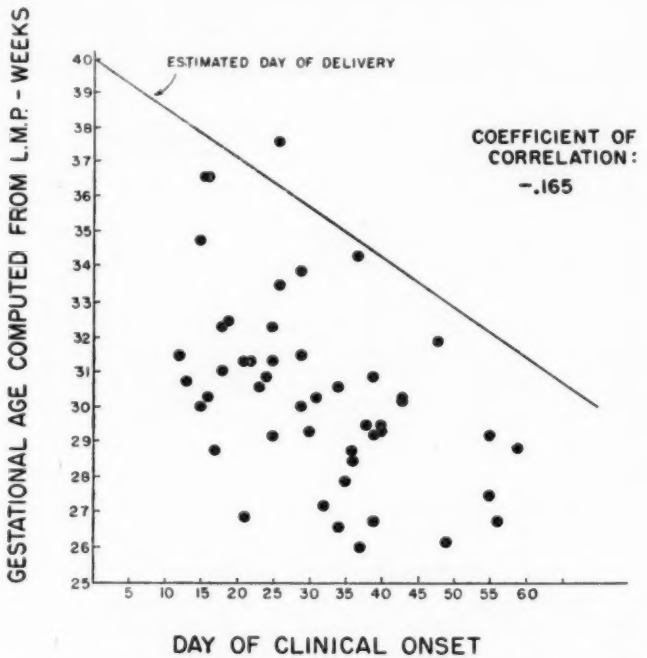

Chart 9.—The correlation of gestational age to day of clinical onset. This could easily have arisen by chance. The onset of retrolental fibroplasia (age in days) in all but one of the infants began before the estimated day of delivery.

COMMENT

The incidence of retrolental fibroplasia has been reported to vary greatly from one year to another in the same hospital and from one hospital to another in the same year.[10] It has been stated that the over-all incidence of the disease has increased

10. (*a*) Kinsey, V. E., and Zacharias, L.: Retrolental Fibroplasia, J. A. M. A. **139**:572, 1949. (*b*) Gilger, A. P.: Retrolental Fibroplasia in Prematurely Born Children, Am. J. Ophth. **32**:917, 1949. (*c*) Dancis, J.; Lewis, J. M., and Guy, L. P.: Retrolental Fibroplasia: Statistical Study with Particular Reference to Effect of Vitamin A, New England J. Med. **245**:402, 1951.

during the last decade.[11] Various changes in the management of the premature infant have purportedly resulted in the eradication of the disease in some nurseries,[4] and a reduction of the severity of the disease in others.[12] We believe it important to define the incidence of the disease in detailed terms, with reference to the population of premature infants "exposed to risk" in a given place and time. Without this knowledge of the natural history of the disease in a nursery, *post hoc* experiences become difficult or impossible to interpret. This study was undertaken to provide further answers to such questions as, "Does the incidence of retrolental fibroplasia vary with time in a manner that cannot be explained by population differences?" and "Does the severity of the disease vary with time in a manner that cannot be explained by changes in medical management?"

This report of the incidence of retrolental fibroplasia has placed emphasis upon two considerations:

1. The diagnosis of retrolental fibroplasia has been made on the basis of changes in the ocular fundi noted during the weekly ophthalmoscopic examination of all infants in the nursery. Those infants who exhibited changes characteristic of the acute phase of the disease and whose retinal lesions regressed to normal were included with the infants having retrolental fibroplasia. Moreover, the final classification of the cicatricial stage of the disease was made with knowledge of the changes which preceded it. With the infant under anesthesia, cicatricial residua were occasionally seen in the far periphery of the retina that might easily have escaped the ophthalmoscopic search of an examiner who had not observed the earlier, acute changes.

2. The frequency distribution of the birth weights and gestational ages [13] of the studied population of premature infants is described in detail. Valid comparison of two groups of premature infants is not possible unless these details are available. The incidence of retrolental fibroplasia clearly varies with the degree of prematurity, and it should be incumbent upon reporters to make an effort to evaluate the degree of prematurity of the infants studied.

The incidence of retrolental fibroplasia varied in a manner that was independent of measurable changes in the population of premature infants in a two-year period. These observations should be extended to include large numbers of surviving infants in different geographical locations.

Further, the incidence varied in a manner that was independent of any known change in the clinical management of these infants during the two years. There was

11. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Am. J. Ophth. **32**:1, 1949.

12. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants: II. Studies on the Prophylaxis of the Disease: The Use of Alpha Tocopheryl Acetate, Am. J. Ophth. **32**:1631, 1949. Campbell, K.: Intensive Oxygen Therapy as a Possible Cause of Retrolental Fibroplasia: A Clinical Approach, M. J. Australia **2**:48, 1951. Hepner, W. R.: Retrolental Fibroplasia in Premature Infants and Kittens, read before the Society for Pediatric Research, Atlantic City, N. J., May 6, 1952.

13. Schlesinger, E. R., and McCaffrey, I.: Incidence of Blindness from Retrolental Fibroplasia, read at the Twentieth Annual Meeting of the American Academy of Pediatrics, Toronto, Canada, Oct. 25, 1951.

no correlation between the time of appearance of the ocular changes and the time of starting administration of medicinal iron, water-soluble polyvitamin preparations, low-fat formulae, antibacterial drugs, or transfusions of blood or plasma. No correlation existed between the time of clinical onset and the duration of administration of these various agents to the affected infants. Regression of the ocular changes occurred in infants who continued to receive iron, water-soluble vitamins, low-fat formulae (with unchanged sodium intake), antibacterial drugs, and transfusions. Regression of the changes occurred in infants who were transferred suddenly from the oxygen-enriched air of the incubator to the atmospheric-air of the bassinet. Moreover, the incidence of the disease increased in the nursery despite unchanged policies concerning oxygen administration, sodium intake, etc. This negative evidence must be weighed against previously published observations that have placed these factors under suspicion as being possibly related to the cause of retrolental fibroplasia.

It should be emphasized that the severity of the disease increased during the second year of the study. Larger numbers of infants with cicatricial residua were discharged during the second year. The numbers whose lesions regressed to normal were unchanged. This change in severity was likewise unrelated in any known manner to the details of management noted in the preceding paragraph.

Finally, it was of special interest to note that the severity of the disease was unrelated to birth weight or gestational age. We have concluded that, although the incidence of the disease was greater among the most premature infants, once the process began, the course of the disease was unrelated to the degree of prematurity. It is difficult to interpret this phenomenon, and probably unwise to base far-reaching conclusions upon it. However, if this previously unmentioned characteristic of the disease can be confirmed by further observation, it must be given considerable weight by future interpreters.

This last observation, the dissociation of severity and the degree of prematurity, and the inverse correlation between birth weight and the age at clinical onset of the disease remain as the two most challenging observations upon completion of this study.

SUMMARY

The incidence of retrolental fibroplasia was determined by weekly ophthalmoscopic examinations in two premature nurseries in New York City during 1950 and 1951.

1. The incidence of retrolental fibroplasia was not related to cutaneous hemangiomata, exclusive of a common inverse relationship to birth weight.

2. An inverse relationship was found between birth weight and the age at which the first fundus changes appeared. No significant relationship existed between gestational age at birth and time of clinical onset of the disease.

3. There was no significant correlation between the time of clinical onset and the time when oxygen therapy was discontinued when the effect of birth weight was eliminated.

4. The frequency distributions, with respect to birth weight, gestational age, and the two factors simultaneously, of surviving infants whose birth weight was less than 1,700 gm., were not significantly different in the two years under comparison.

5. The details of postnatal care remained unchanged during the two years.

6. The incidence of retrolental fibroplasia was higher in 1951 than in 1950, confirming the observation of Dancis and associates.[10c]

7. Severe cases were more numerous in 1951.

8. The severity of the disease was unrelated to the degree of prematurity.

The technique of ophthalmoscopic examination of premature infants is described in detail.

Dr. John W. Fertig, Professor of Biostatistics, of Columbia University School of Public Health, gave advice and criticism.

NONDIABETIC LIPEMIA RETINALIS

Report of a Case

W. G. EVERETT, M.D.
PITTSBURGH

LIPEMIA retinalis was first described by Heyl [1] in 1880. The pathognomonic quality of this phenomenon must certainly have impressed him when he wrote, "The moment my eye caught the details of the fundus, I saw the remarkable appearance which I shall endeavor to describe." Duke-Elder [2] describes the condition as unmistakable. He states:

> The change in colour of the retinal vessels is seen first in the periphery where they become hazy and slightly milky, and gradually the appearance spreads up towards the disc, the arteries and the veins in the average cases becoming flat and ribbon like and assuming a uniform appearance as if filled with milk, although in some cases a salmon-colour merging into cream is retained on or near the disc. In other cases the appearance is yellowish, but in all cases the light reflex becomes diffuse or is lost, and frequently yellowish-white stripes accompany both arteries and veins toward the periphery as if there were a fatty infiltration of the perivascularis. At the same time the disc and ground of the fundus remain normal. In the worst cases the milky colour deepens to become a dull ivory and the fundus assumes a lighter hue due to similar changes in the choroidal vessels.

Lipemia retinalis is a manifestation of a high degree of hyperlipemia. The latter term, as pointed out by Thannhauser,[3] is to be reserved for an abnormal increase in the neutral fat in the serum, in contradistinction to hyperlecithemia and hypercholesterolemia. If the hyperlipemia is sufficiently intense, it becomes evident in the retinal vessels and is perceptible ophthalmoscopically. Thannhauser [3] divides hyperlipemia into physiologic, or postprandial, hyperlipemia; retention hyperlipemia, as characterized by an essential, or idiopathic, hyperlipemia, and transportation hyperlipemia, as seen in severe diabetes, usually associated with diabetic acidosis. Hyperlipemia has also been seen in chronic alcoholism, starvation, severe anemias, leukemias, lipid nephrosis, toxic liver damage, asphyxia, nephrotic state of glomerulonephritis, renal-vein thrombosis, and glycogenosis (von Gierke's disease).[4]

Lipemia retinalis is observed when the neutral fats of the blood serum are in the range of 2,500 mg. per 100 cc. or greater. The level at which the change occurs is apparently not critical but varies from 2,000 to 4,500 mg. per 100 cc. Most observers report that the lipemia disappears at a lower serum neutral fat level than that at

From the Departments of Ophthalmology and Pediatrics of the University of Pittsburgh School of Medicine and the Children's Hospital.

1. Heyl, A. G.: Tr. Am. Ophth. Soc. **3**:54, 1880.

2. Duke-Elder, W. G.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, Vol. 3, p. 2743.

3. Thannhauser, S. J.: New England J. Med. **237**:515, 1947.

4. (*a*) Thannhauser.[3] (*b*) Elwyn, H.: Diseases of the Retina, Philadelphia, The Blakiston Company, 1946, p. 106.

which it first appears. Hyperlipemic serum may be grossly turbid without characteristic changes in the retinal vessels. The milky quality of lipemic serum is due to the presence of lipid droplets of a size greater than ¼ wave length of visible light. Under ordinary circumstances the lipids of the serum are in colloidal suspension and nonvisible. In a lipemic serum the colloidally suspended lipids coalesce to form visible droplets, and a milky serum results.

An increase in the serum neutral fat to a state of supersaturation has usually been attributed as the cause of the formation of visible lipid droplets and a milky serum. Boyd [5] stresses the importance of factors additional to an increase of neutral fat. He found a relative insufficiency of phospholipid in relation to the total serum lipid in lipemic sera, even though the phospholipid was elevated. Boyd [6] also presents a case in which there was a normal total serum lipid content with an abnormally low serum phospholipid level and a milky serum. Ahrens and Kunkle [7] discuss the role of phospholipids in relation to the colloidal state of the neutral fats in serum and present a study of 36 lipemic and clear sera with a quantitative comparison of their component lipid patterns. These authors found the normal range of the ratio of phospholipid to total lipid in 25 sera to be 0.30 to 0.40. A study of 19 lipemic sera revealed a significantly reduced phospholipid-total lipid ratio or a relatively decreased phospholipid value.

Since the description of lipemia retinalis in 1880 by Heyl,[1] approximately 65 cases have been reported, predominantly of diabetic patients. An additional 12 cases have been reported in nondiabetic patients. Wagener [8] reported the first instance of nondiabetic lipemia retinalis in 1922. Since that time two cases have been presented by Holt, Aylward, and Timbres,[9] in 1936 and 1939 respectively; one by Bernstein,[10] in 1939; one by Goodman,[11] in 1940; one by Kauffman,[12] in 1943; one by Lepard,[13] in 1944; one by Grossman and Hitz,[14] in 1948; three by Groom and Rucker,[15] in 1950, and one by Dunphy,[16] in 1950.

REPORT OF CASE

C. R., a boy aged 3½ years, was admitted to the Children's Hospital of Pittsburgh for tonsillectomy in April, 1952, with the chief complaints of recurrent fever and convulsions.

Past History.—The child had had numerous generalized convulsions, beginning in August, 1951. Since that time the child had been studied at three other hospitals, where the routine findings had been normal. A spinal puncture, pneumoencephalogram, roentgenograms of the skull, and blood studies had also been reported as showing nothing abnormal. Some irregularities were reported in the electroencephalogram. The child had received diphenylhydantoin

5. Boyd, E. M.: Tr. Roy. Soc. Canada **31**:11, 1937.
6. Boyd, E. M., and Connell, W. F.: Arch. Int. Med. **61**:755, 1938.
7. Ahrens, E. H., Jr., and Kunkle, H. G.: J. Exper. Med. **90**:409, 1949.
8. Wagener, H. P.: Am. J. Ophth. **5**:521, 1922.
9. Holt, L. E., Jr.; Aylward, F. X., and Timbres, H. G.: J. Clin. Invest. **15**:451, 1936; Bull. Johns Hopkins Hosp. **64**:279, 1939.
10. Bernstein, S. S.; Williams, H. H.; Hammel, F. C.; Shepard, M. L., and Erickson, B. N.: J. Pediat. **14**:570, 1939.
11. Goodman, M.; Shuman, H., and Goodman, S.: J. Pediat. **16**:596, 1940.
12. Kauffman, M. L.: Am. J. Ophth. **26**:1205, 1943.
13. Lepard, C. W.: Arch. Ophth. **32**:37, 1944.
14. Grossman, E. E., and Hitz, J.: Arch. Ophth. **40**:570, 1948.
15. Groom, J. J., and Rucker, C. W.: Am. J. Ophth. **33**:1238, 1950.
16. Dunphy, E. B.: Am. J. Ophth. **33**:1579, 1950.

and trimethadione but continued to have convulsions. In December, 1951, 4½ months prior to the present hospitalization, the child was placed on a high-fat diet with a ketogenic-antiketogenic ratio of 4.0. The diet was 84% fat by weight. The family reported that the child did well on this regimen except for one period of fever and tonsillitis associated with a generalized convulsion. Three weeks prior to the present admission a tonsillectomy for recurrent tonsillitis was advised by the attending pediatrician.

Family History.—There was no family history of diabetes, tuberculosis, heart disease, convulsive disorders, or xanthomatous disease.

Physical Examination.—The patient was a well-developed, well-nourished boy, 3½ years of age. He was afebrile. His physical measurements were not abnormal. The forehead and chin revealed several bruise marks resulting from falls during convulsive seizures. The nasal mucous membrane was red and boggy. The pharynx revealed reddened and greatly enlarged tonsils. The heart and lungs were normal. The blood pressure was 108/70. The abdomen was soft, flat, and not tender. The liver, spleen, and kidneys were not palpable. Peristalsis was normal. A careful neurologic examination revealed nothing abnormal. There was no evidence of xanthomatosis.

Ocular Examination.—There was no apparent visual disturbance. Externally the eyes were normal. Ocular tension was normal to finger palpation. The fundi showed characteristic changes of lipemia retinalis. The vessels had a waxy-cream color. They appeared to be flattened, and their caliber was increased. The arteries and the veins were almost indistinguishable. Peripherally, the light reflex of the vessels was absent. The cream-like appearance of the vessels assumed a slight pinkish tint for about 1 disk diameter beyond the disk. These changes were repeatedly observed day and night.

Laboratory Data.—The peripheral blood was milky throughout the patient's stay in the hospital. Repeated urinalyses failed to reveal sugar but showed a 3+ reaction for acetone and a 3+ reaction for diacetic acid. The red blood cell count was 3,550,000 per cubic millimeter; the white blood cell count, 8,950 per cubic millimeter, with a normal differential count; carbon dioxide, 14.2 milliequivalents per liter; chlorides, 94.4 milliequivalents per liter; serum cholesterol, 1,280 mg. per 100 cc.; serum phosphorus, 3.71 mg. per 100 cc., and nonprotein nitrogen, 26 mg. per 100 cc. A second cholesterol determination on the seventh hospital day showed 582 mg. per 100 cc. (after 24 hours of fasting). Serum lipid determinations revealed 2,400 mg. total lipids, 500 mg. phospholipid, and 700 mg. neutral fat, per 100 cc. The phospholipid-total lipid ratio was 0.21, a value in keeping with the changes in lipemia reported by Ahrens and Kunkle.[7] The cephalin flocculation test gave a negative result in 48 hours. The Kahn reaction was negative. The roentgenogram of the chest showed a normal condition.

Hospital Course.—The child was admitted for tonsillectomy only, and not for studies on the cause of his convulsions, as these had been adequately carried out elsewhere. The ketogenic diet, yielding 927 Cal. and consisting of 6 gm. carbohydrate, 12 gm. protein, and 95 gm. fat, was followed while the child was hospitalized. The tonsillectomy was performed on the fifth hospital day. The child had nothing by mouth for 24 hours prior to and immediately following tonsillectomy. After this brief period of fasting the lipemia retinalis disappeared, although the serum remained grossly lipemic. In the first two cases of Groom and Rucker [15] the lipemia retinalis was observed to disappear in two and four days, respectively, with the patients on low-fat diets. Dunphy [16] reports that the lipemia retinalis disappeared in his case in a few days on two different occasions after institution of a low-fat diet. In the case reported by Grossman and Hitz [14] the lipemia retinalis was said to clear in five days with a low-fat diet.

The postoperative course of this patient was uneventful. The child had several petit mal convulsions and an occasional grand mal seizure during his hospital stay. He was discharged on the eighth hospital day.

Livingston [17] states that in over 500 patients placed and followed on a ketogenic diet similar to the diet of this patient, lipemia retinalis was never observed.

17. Livingston, S.: Personal communication to the author.

SUMMARY

Previously reported cases of nondiabetic lipemia retinalis are cited. A case of nondiabetic lipemia retinalis in a patient whose diet was high in fat is reported. The high-fat content was shown to play a part in the production of persistent lipemia retinalis as long as the diet was followed. The lipemia retinalis was seen to disappear in this patient after 24 hours of starvation. Such a diet may cause lipemia retinalis in some persons.

Drs. R. R. Macdonald and W. F. Stengel permitted the report of this case, and Dr. Campbell Moses, Director of the Addison H. Gibson Laboratory, made the special lipid studies.

PTERYGIUM PROBLEMS IN THE CANAL ZONE

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AND
CAPTAIN FREDERICK R. CARRIKER
MEDICAL CORPS, UNITED STATES ARMY

THE MANAGEMENT of pterygia in the tropical area of the Canal Zone is one of the paramount problems confronting the ophthalmologist.

During the years 1950 and 1951 a total of 170 patients had surgical removal of pterygia at Gorgas Hospital. Of this group only 18% were American white persons; 82% were Panamanians employed by the Canal Zone. The Panamanian group included Jamaicans and scattered units from other Central-American countries now living in Panama. Only one-fourth of this group were females. Sixty-five per cent of these patients were between the ages of 20 and 40. A Negro girl aged 7 years was operated on in this series. Fifty-six patients had an operation for pterygium on the right eye, 59 on the left eye, and 53 on both eyes. On 100 patients a McReynolds or a modified McReynolds transplantation was done. A resection was performed on 70 patients. The resection type of surgery included a simple resection by the method of D'Ombrain,[1] Sugar,[2] McGavic,[3] or King.[4] Fifteen per cent of the 170 patients had operations for recurrent pterygium. In 60% of these patients with recurrences the pterygium had returned within two years.

ETIOLOGY

The literature reveals two conflicting views concerning the etiology of pterygia: that of a degenerative process and that of a chronic inflammation of the conjunctiva due to irritation from the elements—the wind, sand, and sun.[4a] Sugar [2] is of the opinion that pterygium develops from a pinguecula and points out the similarity in the histological pictures. He agrees with Duke-Elder [5] that the process is primarily a degenerative one. We believe that the pterygium is a result of chronic conjunctival inflammation, as stated by Kamel.[6] The degenerative picture present is apparently secondary to the initial inflammatory process. In observing a so-called

From Gorgas Hospital, Ancon, Canal Zone.

1. D'Ombrain, A.: Surgical Treatment of Pterygium, Brit. J. Ophth. **32**:65 (Feb.) 1948.

2. Sugar, H. S.: A Surgical Treatment for Pterygium Based on New Concepts as to Its Nature, Am. J. Ophth. **32**:912 (July) 1949.

3. McGavic, John S.: Surgical Treatment of Recurrent Pterygium, Arch. Ophth. **42**:726 (Dec.) 1949.

4. King, J. H., Jr.: The Pterygium: Brief Review and Evaluation of Certain Methods of Treatment, Arch. Ophth. **44**:854 (Dec.) 1950.

4a. Gerundo, M.: On the Etiology and Pathology of Pterygium, Am. J. Ophth. **34**:851 (June) 1951.

5. Duke-Elder, W. S.: Text-Book of Ophthalmology Vol. 2, St. Louis, C. V. Mosby Company, 1940, p. 2,000.

6. Kamel, S.: Pterygium: Its Nature and a New Line of Treatment, Brit. J. Ophth. **30**:549 (Sept.) 1946.

malignant pterygium, where a fleshy vascular growth progresses fairly rapidly over the cornea, one is impressed with the vascular activity and the growth, which fits the picture of an inflammatory process rather than a degenerative process.

In our series of patients it is noted that 65% were between the ages of 20 and 40. The age grouping fits in with an inflammatory process rather than with a degenerative process. A 7-year-old colored girl had a large, fleshy pterygium removed from her eye. This case is especially interesting, since some authors believe that pterygia are never seen in children.[7]

Etiologic Factors.—In the Canal Zone it is very hard to explain the discrepancy between the incidence of pterygia in the American population and in the Panamanian group. The American group eligible for treatment at Gorgas Hospital (Canal Zone employees, 4,474; Army civilian employees, and Army military personnel) is actually larger than the Panamanian group, of 15,120, eligible for treatment at Gorgas Hospital; yet there are roughly three times as many cases of pterygium in the Panamanian group as in the United States group.

The main difference between these two groups in the Canal Zone is in their standard of living. The diet of the Panamanian group is similar to that found throughout Central America, in contrast to the diet of the American group living in the Canal Zone, which is similar to that in middle-class families in the United States. Therefore we believe that the type of diet of the Panamanian group may be an important etiologic factor in the formation of pterygium.

Another factor is that the Panamanian group is primarily of the laboring class, who as a whole are exposed to the various climatic factors of the tropics, such as glare, dust, and wind. With the humidity and the heat of the tropics, sweating is usual in any type of physical effort, with the consequence that perspiration runs into the eyes, resulting in conjunctival irritation and the greater frequency of conjunctival infection.

Whether glare in itself is an etiologic factor is hard to determine. On the Isthmus there is a group of American Canal pilots who work day after day under constant glare from reflection of the sun on the water while they are piloting ships through the Canal. The significant difference is that, in contrast to the Panamanian group, the Canal pilots as a whole are well nourished and when exposed to the glare use protective sunglasses. Surprisingly, the incidence of pterygium in this group is negligible.

Factors in Recurrence.—It is noted above that 15% of the group had surgical treatment for recurrent pterygium. It is our belief that pterygia recur for the following reasons: (*a*) inadequate surgery; (*b*) stimulation of an excessive inflammatory process at the surgical site, (*c*) reexposure of the patient to the same etiologic factors.

TYPES OF PTERYGIA

Hilgartner and associates [8] divide pterygia into two types: (*a*) the small, slow-growing, rather avascular pterygium, with a flat, more or less whitish-gray head and practically no cap, and (*b*) the highly vascular, thick, somewhat inflamed growth,

7. Berens, C.: The Eye and Its Diseases, Ed. 2, Philadelphia, W. B. Saunders Company, 1949.

8. Hilgartner, H. L.; Wilson, R. T., and Wilson, J. D.: Surgical Treatment of Pterygia Followed by X-Ray Therapy to Prevent Recurrence, Am. J. Ophth. **31**:667 (June) 1948.

with elevated head and a very definite cap, which extends some distance beyond the head onto the cornea. This clinical distinction is important in determining the best type of treatment. The first (*a*) type of pterygium may very well be treated with success by a McReynolds transplantation or by a simple excision type of operation that does not leave a bare scleral area. This may explain why successful removal of pterygia is reported in the literature with certain surgical procedures and why high recurrence rates are noted by others when using the same technique. In the Canal Zone one is concerned primarily with the second (*b*) type of pterygium.

SURGICAL TREATMENT

King [4] is of the opinion that every pterygium should be removed surgically, the earlier the better. This is certainly true of the second type of pterygium, which is so common in the tropics. However, in the older age groups one does see small, atrophic, avascular pterygia with slight encroachment on the cornea, of many years' duration. We believe that this type of pterygium should not be treated surgically. We have noted that pterygia of this order were stimulated by the surgical removal, with the recurrence of a pterygium of the *b* type, which demanded a more radical operation.

The *b* type of pterygium should be removed as early as possible. We do not believe, as do some other authors, that a simple excision or a McReynolds pterygium operation is indicated or successful with this type of pterygium. Surgically, it is desirable that the pterygium be completely removed from the cornea and that the vascular tissue of the episclera be removed with the head of the pterygium, so that the conjunctiva may heal by rapid epithelization, and not by granulation of the episcleral tissue. This operation should be accomplished with minimal trauma or irritation. In fulfilment of these requirements, we believe that the following routine is valuable in treatment of recurrent and also of type *b* pterygia.

1. Instillation of antibiotics into the conjunctival sac two or three days prior to operation. This tends to limit the possibility of a secondary infection, which would promote healing by granulation.

2. Use of one of the "bare-sclera" techniques (D'Ombrain,[1] Sugar,[2] McGavic,[3] and King [4]). These surgical procedures have in common the complete removal of the head of the pterygium and removal of the episcleral vascular tissue, leaving a bare sclera at the limbus.

3. Postoperative use of cortisone eye drops. Starting on the first postoperative day, 1 drop of the cortisone suspension, 1.0 cc. containing 25 mg., is placed every three hours for four days in the eye operated on, and the dose is then gradually decreased, the rate depending upon the appearance of the eye. Since the beneficial effects of the adrenocortical hormones on ocular disease appear primarily to be a control of the inflammatory and exudative phases,[9] we believed that cortisone would be a valuable adjunct in reducing the tendency of the surgical wound to heal by formation of granulation tissue, and thus allow healing by epithelization primarily.

It is our impression from following 30 cases of pterygium after operation that the use of cortisone has been extremely beneficial in reducing the tendency of a

9. Woods, A. C.: Clinical and Experimental Observation on the Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325 (Sept.) 1950.

pterygium to recur. It is too early in our series, however, to present valid statistical data. The action of cortisone will inhibit an inflammatory reaction, inhibit the formation of granulation tissue, and thus promote healing by epithelization.

4. Postoperative use of antibiotics.

5. Radiation therapy. Soft x-radiation is a valuable adjunct in suppressing the formation of granulation tissue when it appears that cortisone in itself will not control it. We also use radiation to reduce the vascularization of the corneal wound.

6. Postoperative treatment. This includes (*a*) refraction; (*b*) use of sunglasses; (*c*) hygienic instruction in daily care of the eyes; (*d*) improvement in and supplementation of diet, and (*e*) possible change of occupation.

The above factors are all related in keeping the patient from being reexposed to possible etiologic factors in the production of a recurrence of his pterygium. We have recommended to some patients a change of occupation when they are exposed to many irritative factors and have had several recurrences of their pterygia. It is thought that the course of treatment outlined has been beneficial in reducing the number of recurrences of pterygium in the Canal Zone.

SUMMARY

The incidence and severity of pterygia in the tropical Canal Zone produce a serious therapeutic problem.

It is thought that the etiology of pterygium is linked with chronic conjunctival inflammation.

Improper nutrition is suggested as a possible etiologic factor in the formation of pterygia.

Pterygia can occur in a relatively young age group. The case of a 7-year-old Negro girl with a pterygium is noted.

It is believed that pterygia recur because of inadequate surgical treatment, an excessive postoperative inflammatory process, and the reexposure of the eye to the same etiologic factors after operation.

Clinical distinction of two types of pterygia is of value in determining treatment.

It is advisable not to operate on small, atrophic, nonprogressive, avascular pterygia in persons of the older age group.

A definite surgical routine, with removal of the episcleral tissue, leaving a bare sclera area, followed by the use of cortisone in suppressing the formation of granulation tissue, is valuable in reducing the rate of recurrence after pterygium surgery.

RETINOBLASTOMA SUCCESSFULLY TREATED WITH X-RAYS; NORMAL VISION RETAINED AFTER THIRTY-FOUR YEARS

Second Report on a Case

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BOSTON

THIS CASE was first reported by me[1] in 1921, three years after treatment. The patient, at the age of 17 months, was referred to me on Nov. 22, 1917, by Dr. John Kerrigan. On Nov. 24 the right eye was removed by him and sent to me for pathological examination. I found it three-fourths filled with a retinoblastoma, containing many rosettes. The tumor had not involved the optic nerve or choroid. On May 2, 1918, the patient was again referred to me by Dr. Kerrigan.

I now found in the retina of the left eye in the lower outer quadrant a white opaque elevated mass, irregularly oval in shape and about 4 P.D. in greatest diameter. It did not reach to the limit of the ophthalmoscopic field. Near this mass, but entirely separate from it, were two small white spots each about ¼ P.D. in size. The patient was immediately referred to Dr. Liebman for x-ray treatment of the left eye, with instruction for sub-erythema dosage to be employed and the exposures to be made through a perforated lead plate so as to protect the lens and anterior part of the eye. Dr. Liebman gave the first treatment on the same day, a sub-erythema dose through a 5 mm. aluminium filter. After this, similar treatment was given once a week for three weeks, and on June 6th, June 27th, August 1st, November 1, 1918 and on January 17, 1919.

The patient was seen by me at intervals of one or two months, but without general anaesthesia it was impossible to make a careful study of the ophthalmoscopic appearances, only glimpses of the tumor as a rule being obtained. On May 23, 1918 I noted that the tumor appeared less white. On Aug. 1st, the tumor appeared translucent and smaller in size. October 19, 1919, the patient was examined under ether narcosis. The tumor appeared translucent, somewhat smaller and less elevated. The white spots near it had completely disappeared.

April 4, 1921, a good view of the tumor was obtained. It appeared only slightly elevated, gray and translucent, and somewhat smaller than the original tumor. Its outline was fairly sharp in places, but not easily seen. No traces of the white spots could be found. A few small vessels traversed it. The retinal vessels became tortuous as they approached the tumor.

The last note of the first report was dated June 8, 1921. The appearance at the site of the tumor was unchanged. The lens was still clear. Vision, as determined by picture charts, was normal. On Dec. 20, 1922, when the boy was 6 years old, I first noted a small oval opacity at the back of the lens, somewhat temporal to the posterior pole.

The patient has subsequently been seen seven times. On July 9, 1943, vision with a +0.50 sphere was 20/20. His latest visit, after an interval of nine years, was on April 19, 1952, when he was nearly 36 years of age, and 34 years after the first x-ray treatment. The tumor site and the posterior cortical cataract were still

1. Verhoeff, F. H.: Glioma Retinae Treated by X-Rays with Apparent Destruction of the Tumor and Preservation of Normal Vision, Arch. Ophth. **50**:450, 1921.

unchanged in appearance. Vision (left eye) was 20/30+; with a correction of +0.50 sph. ⌒ —0.75 cyl., ax 90 it was 20/20. The patient stated that his general health was excellent.

Reese,[2] in his recent textbook, states in regard to my case:

> In particular, the patient reported by Verhoeff and the one reported by Fleischer received such small doses that the results must be considered to be examples of spontaneous regression and not cures by irradiation. There are more reports in the literature of spontaneous regression than of cures by irradiation. None of the authors has reported further cures. If a permanent cure could be obtained consistently by such techniques and dosages, the successful treatment of retinoblastoma by irradiation would be a simple matter. If, in the treatment of any disease, the successful therapeutic result obtained in a single instance by a particular method cannot be consistently repeated, the report of a successful cure is interesting only as a medical curiosity.

In spite of this contention, Reese then states:

> Retinoblastoma is a fairly radiosensitive tumor; it can be completely devitalized by a dose of irradiation well tolerated by the skin, subcutaneous fat, bone, nerve, and similar tissue. There would, therefore, be little difficulty in sterilizing such a tumor except for the fact that it is not readily accessible to irradiation and lies close to the radiosensitive ciliary body, lens, and cornea.

It is to be noted that the tumor in my case was small, situated at the equator on the temporal side, and hence readily accessible to irradiation. Before reaching the tumor, the x-rays did not penetrate the bony wall of the orbit, as in Reese's cases. Moreover, the dose Dr. Liebman employed in my case was the same as that he had found effective in treating some epitheliomata of the lids. The fact that a small posterior cortical cataract developed in spite of protection by a lead plate also speaks for the potency of the x-ray treatment.

Reese states: "At least 12 well-authenticated cases in which cure was spontaneous have been reported in the literature." Assuming that the lesion in each of these cases was really a retinoblastoma, it would seem at first glance that these cases present overwhelming evidence that my case was one of spontaneous regression. But investigation of these cases shows that the evidence they provide is overwhelmingly to the contrary, for in each case there was a residuum consisting of chalky material and/or chorioretinal atrophy with pigmentary changes. In not a single case did the tumor simply melt away, as in my case, and leave the site almost normal in appearance. It is impossible for me to believe that a retinoblastoma could disappear in this fashion spontaneously, but it is well known that certain tumors elsewhere, notably lymphomata, thus disappear in response to x-ray treatment.

If Reese was correct in his conclusion that my case was one of spontaneous regression, he would be more than justified in belittling its importance. But since, for the reasons given above, it was not such, I regard it as of considerable importance. It proves that a small retinoblastoma, free from calcification and easily accessible, can be made to disappear with a dose of x-rays harmless to the eye except for possible damage to the lens. My case dates as far back as 1918 and was only the third successful case reported. I feel sure that, directly or indirectly, it encouraged others, including Reese, to undertake and to attempt to improve the x-ray treatment of retinoblastoma.

The first case of retinoblastoma successfully treated by irradiation was that of Hilgartner, cited by Schoenberg.[3] The enucleated eye was not examined micro-

2. Reese, A. B.: Tumors of the Eye, New York, Harper & Brothers, 1951, p. 109.

3. Schoenberg, M. J.: A Case of Bilateral Glioma of the Retina Apparently Arrested in the Non-Enucleated Eye by Radium Treatment, Arch. Ophth. **48**:485, 1919.

scopically. This case is not mentioned by Reese, and I know nothing as to its subsequent history. The second case was reported by Schoenberg in 1919 [3] and in 1927.[4] This case ultimately came under the observation of Reese, who includes it as one of his four cases of postirradiation sarcoma. He states that in 1943 a scar-tissue sarcoma developed in the temporal region over the site of the temporal portal used in the treatment of the ocular tumor and proved fatal in 1944. According to Schoenberg's reports, the original treatment was by radium; the best vision recorded was 20/100, and after a cataract extraction in 1926 the vision with cataract glass was only 15/100. Dr. Reese informs me that the hospital records of this case were destroyed in 1947, but he recalls that they showed the treatment to have been chiefly with x-rays and that when he tested the vision it was 20/30.

So long as my patient lives and maintains good vision, he will continue to hold the record for duration of good vision after irradiation of retinoblastoma. The result in this case seems to be better than any reported by Reese. He has employed x-ray treatment in 55 cases, but only in 19 cases have the patients been followed for five years or more. Of these, seven died of the disease, six lived but were blind, and six had vision of 20/200 or better. My case suggests that his visual results might have been better and his bad results no worse if he had employed a weaker dose, at least in selected cases. Reese [5] himself states: "We believe that the dose might be reduced to even 4,000 to 5,000 r $\times$ 2." This would mean the employment of about one-half his present dose.

4. Schoenberg, M. J.: Report on a Case of Bilateral Glioma of the Retina, Cured in the Non-Enucleated Eye by Radium Treatment, Arch. Ophth. **56**:221, 1927.

5. Reese,[2] p. 114.

SYMPATHIZING EYE IN SYMPATHETIC OPHTHALMIA

A Pathologic Study

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BROOKLYN

HISTOLOGIC examinations of eyes secondarily involved in sympathetic ophthalmia have been reported infrequently. Recently Haik and his associates,[1] in reviewing sympathetic ophthalmia, commented that "no case seems to have been recorded in the American literature." These authors found the entire literature on the "sympathizing eye" surprisingly scant. Loewenstein,[2] in 1945, had collected records of 19 examinations, most of which had been made in Germany before 1900, and to them he added 4 cases of his own. Thirteen other cases were recorded by Greeves [3] in 1948. Haik and his co-workers, after reviewing the 18 cases in the British journals, pointed out that most of the sympathizing eyes had been removed late in the course of the disease. They implied that in some cases at least, the condition may have been bilateral endophthalmitis, and not true sympathetic ophthalmia.

The case to be discussed furnished an example of what I believe to be the classic lesion of sympathetic ophthalmia in a florid state in the sympathizing eye. Inflammation in the exciting eye followed promptly an extracapsular cataract extraction; enucleation of the exciting eye followed by about three weeks the onset of inflammation in the second eye. Because of pain and complete loss of vision, the sympathizing eye was enucleated five weeks after it became inflamed.

REPORT OF A CASE

S. K., aged 76, a patient in the Brooklyn Hebrew Home and Hospital for the Aged, had bilateral cataract and underwent an extracapsular extraction on the right eye on April 10, 1945. As much cortical material as possible was washed out of the anterior chamber. The eye promptly became red. The inflammation persisted, and pain developed and gradually increased. In the latter part of June, approximately 10 weeks later, the left eye, in which there was an immature cataract, became inflamed. Inasmuch as there was by then only light perception in the right eye (the one that had been operated on), its enucleation to prevent sympathetic ophthalmia was advised, but not until July 3, 12 weeks after operation and 3 weeks after the onset of inflammation in the second eye, was enucleation permitted. Unfortunately, this eye was lost.

From the Departments of Pathology of the Brooklyn Hospital and the Brooklyn Eye and Ear Hospital.

1. Haik, G. M.; Waugh, R. L., Jr., and Lyda, W.: Sympathetic Ophthalmia: Similarity to Bilateral Endophthalmitis Phacoanaphylactica, A. M. A. Arch. Ophth. **47**:437, 1952.

2. Loewenstein, A.: The Sympathizing Eye, Tr. Ophth. Soc. U. Kingdom **65**:219, 1945.

3. Greeves, R. A.: A Contribution to the Microscopic Anatomy of the Sympathizing Eye, Brit. J. Ophth. **32**:545, 1948.

The left eye continued to be inflamed in spite of all the usual therapeutic measures and became increasingly painful. By July 23, approximately five weeks after the first appearance of inflammation, vision was reduced to light perception, and this (the sympathizing) eye was enucleated and referred to me by Dr. Julius M. Dan, to whom I am indebted for the clinical data.

Pathologic Examination.—Gross Findings: The left eye was received in Bouin's solution. It measured 22 mm. in its greatest anteroposterior dimension and 26 mm. transversely at the equator, being somewhat short and broad. Calottes were cut parallel to the horizontal meridian in such a way as to open the anterior chamber. The vitreous was semiopaque and had been coagulated, presumably, by the fixative. The retina and choroid were partially detached by pearly fluid, which also had coagulated. The choroid was irregularly thickened. The lens could be seen in a relatively normal position. No further details could be made out. The eye was embedded in pyroxylin.

Microscopic Findings: Sections were prepared through and parallel to the horizontal meridian and were stained by the hematoxylin-eosin method. They showed a generalized

Fig. 1.—Horizontal meridional section, showing great thickening of the uvea, detachments of the retina, choroid, and ciliary body, and presence of albuminous exudate in the chambers and spaces. The angle of the anterior chamber is closed. The lens is intumescent, asymmetrical, and cataractous. The optic disk is cupped. Photograph slightly retouched.

granulomatous inflammation of the uvea, characteristic of sympathetic ophthalmia. There was nonsuppurative inflammatory exudate in all the chambers. The angle of the anterior chamber was closed by a broad anterior peripheral adhesion of the iris to the posterior surface of the cornea. Except for chemosis at the limbus, the cornea was unremarkable. There was also a wide posterior pupillary synechia between the iris and the lens capsule. The lens was the seat of advanced cortical and nuclear degeneration, with liquefied substance and Morgagnian droplets intervening between separated lens fibers. There was no evidence of rupture of the capsule (Fig. 1).

The retina had remained in close contact with the choroid over much of its extent; in some areas there were obviously old adhesions. Elsewhere the retina was separated (between the layer of rods and cones and the pigmented-epithelium layer), suggesting that detachment occurred wherever the retina had not previously been anchored by adhesions. The choroid and ciliary body were also partially detached. There was mild nongranulomatous inflammation

in the retina and optic nerve, consisting of lymphocytic infiltration, which was chiefly perivascular. The optic disk was deepened, and the lamina cribrosa bowed backward excessively. The vasculature in general was sclerotic. The anatomic diagnoses were listed as follows in an attempt to differentiate what I conceived to be the changes attributable to the sympathetic ophthalmia from antecedent, and probably unrelated, conditions:

1. Sympathetic ophthalmia in sympathizing eye
   - (*a*) Uveitis of distinctive type
   - (*b*) Detachment of retina, partial
   - (*c*) Detachment of choroid and ciliary body, partial
   - (*d*) Adhesions of iris, anterior and posterior
   - (*e*) Retinitis and optic neuritis, mild
   - (*f*) Glaucoma, acute, secondary
2. Arteriosclerosis, generalized
3. Retinochoroiditis, healed
4. Cataract, senile

Presumptive Changes in the Exciting Eye.—It may be observed that when the diagnosis of sympathetic ophthalmia is established anatomically, it is almost always based on examination of the exciting eye; it is assumed that the sympathizing eye, if sectioned, would show the same pathognomonic features. In this instance only the sympathizing eye was examined anatomically, and one is tempted to reverse the rule and assume that the exciting eye, if examined, would have shown a process of the same nature as that in the second eye. That assumption, although justified in the main, may lead one into errors, and these chiefly errors of omission. Speculation in this case might encompass the following considerations: 1. The operative wound may have contained incarcerated uveal tissue or lens capsule. 2. There may have been an initial endophthalmitis caused by reaction to cortical substance of the lens, a condition which, I have contended, may occasionally be a precursor of sympathetic ophthalmia.[4] This possibility was suggested by the prompt postoperative inflammation. 3. There may have been various other results of postoperative nonspecific inflammation, not essential components of sympathetic ophthalmia. 4. There would, doubtless, have been a uveitis of granulomatous (exudative and proliferative) type, essentially like that encountered in the sympathizing eye. Unfortunately, it was not possible to confirm or to refute these speculations by actual observation.

LESION OF SYMPATHETIC OPHTHALMIA IN THE SYMPATHIZING EYE

E. Fuchs,[5] who furnished a classic description of the histologic findings in sympathetic ophthalmia in 1905, was probably the first to apply that designation to the anatomic lesion, even in the exciting eye. He predicted that the same lesion would be found in the sympathizing eye, except that it would be free of the changes attributed to injury per se. This prediction has been amply fulfilled. He contended, in opposition to the opinion of Schirmer,[6] that plastic exudation was not a part of the sympathetic inflammation and noted that it was not to be expected in the untraumatized, second eye. This often-cited opinion should not be taken to indicate that the uncomplicated lesion of sympathetic ophthalmia is not in part an exudative inflammatory process. The findings in my case confirm those of many previous observers to the effect that exudation from the blood stream, producing various infiltrations of the tissues and outpourings of fluid and cells into tissue spaces and chambers, is one of the essential features of the process in both the exciting and the sympathizing eye.

4. de Veer, J. A.: Endophthalmitis Phacoanaphylactica and Its Relation to Sympathetic Ophthalmia, Arch. Ophth. **23**:237, 1940.

5. Fuchs, E.: Über sympathisierende Entzündung nebst Bemerkungen über seröse traumatische Iritis, von Graefes Arch. Ophth. **61**:365, 1905.

6. Schirmer, O.: Sympathische Augenerkrankung, Leipzig, Engelmann, 1900.

With this dynamic concept of a unique inflammatory process learned from study of many "exciting" eyes, it is difficult to return to the description of a static picture observed in a single "sympathizing" eye, but that is the principal purpose of this presentation.

The chief abnormality seen was great thickening of the uveal coat, most pronounced at the posterior pole and in the ciliary region (Fig. 1). The process involved infiltrations and granulomatous proliferations, combined in various proportions and varying in composition and structure from field to field.

Iris.—The iris was moderately distorted, being adherent to the cornea peripherally and having a thin, sharp pupillary border, where there were adhesions to the lens. The anterior border layer was thick and black. On its surface were scattered and clumped leucocytes. The lamina propria showed essentially two types of disturbance, which in places were combined,

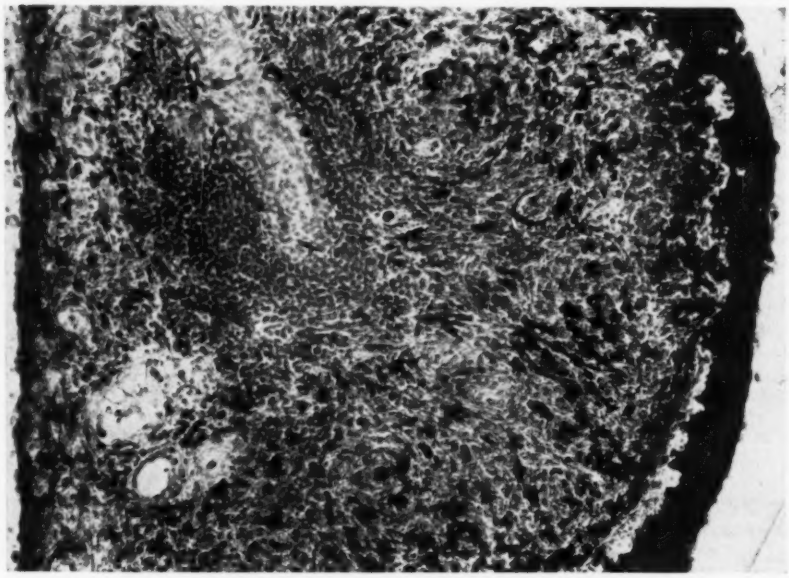

Fig. 2.—Section of the iris. On the left is a thickened, heavily pigmented anterior border layer. Granulomatous proliferative features with melanotic pigmentation predominate posteriorly and anteriorly. A patch of heavy lymphocytic infiltration is seen near the central zone. A number of original iris vessels persist, but the granulation tissue is furnished with newly formed capillaries. The pigmented-epithelium layer is separated by inflammatory exudate from a more anterior, second pigmented layer, probably representing the level of the dilator-muscular layer.

namely, leucocytic infiltration and granulomatous proliferative changes, in which epithelioid cells, densely pigmented macrophages, chromatophores, fibroblasts, and blood vessels combined in various ways to form bizarre configurations. The more purely infiltrative (exudative) features were seen toward the anterior surface, while the productive (proliferative) components predominated posteriorly (Fig. 2). In the iris, as elsewhere in the uvea, lymphocytes formed occasional dense aggregations or nodules. In intervening areas, plasma cells were often more numerous than lymphocytes, and there was a sparse admixture of neutrophilic polymorphonuclear leucocytes. Edema fluid was abundant but was conspicuous only in the less cellular foci.

The pigmented-epithelium layer was somewhat distorted and was raised from the underlying tissue by exudate. There were sparse remnants of the sphincter muscle, but the dilator-muscle layer was only vaguely suggested by a pigmented layer, which perhaps included the bodies of the dilator cells, although no muscular processes could be made out.

Ciliary Body.—Much of what was seen in the stromal layer of the iris was also found in the ciliary body, but here more varied granulomatous configurations were encountered. Perhaps the most distinctive characteristic of the lesion in this region was prominent disruption of the epithelial coats (Fig. 3). The granulomatous components of the inflammation which predominated in the inner portions had invaded the epithelial zone to interrupt and distort the pigmented layer and to separate the nonpigmented from the pigmented layer (Fig. 4).

Fig. 3.—Pars plana of the ciliary body partly detached from the sclera. The epithelial layers have been separated and greatly distorted by inflammatory infiltrations and nodular proliferations. The ora serrata is shown on the right as an angular "step" with an epithelioid nodule beneath it. Leucocytes have infiltrated the ciliary epithelium and have entered the vitreous.

In this region giant cells were numerous—some of them huge and all more or less pigmented. Discrete epithelioid tubercles (nodules) were most conspicuous in the pars plana close to the ora serrata, and were noted both internal and external to the original level of the pigmented epithelium. Other granulomatous foci were so varied in architecture as to defy description. Exudative inflammation predominated toward the outer surface and appeared to have been responsible, at least in part, for partial opening up of the suprachoroidal space (Fig. 3),

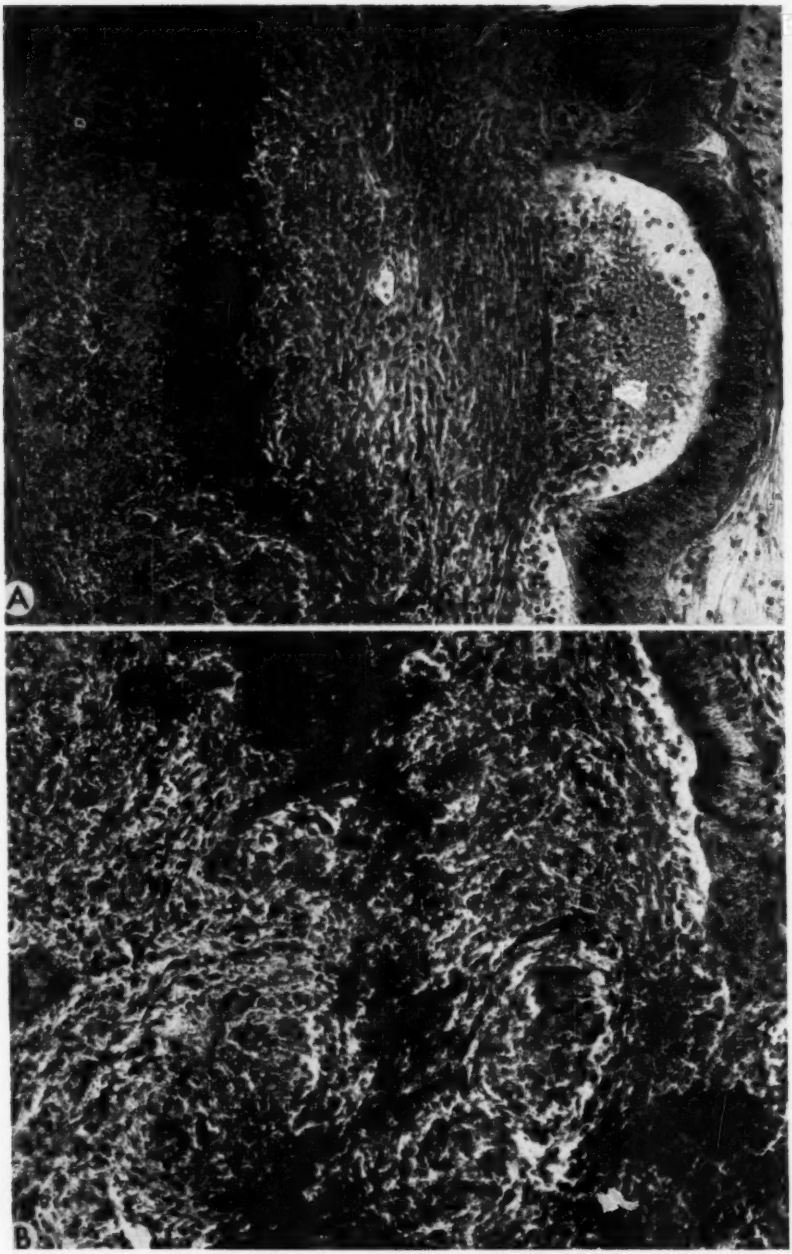

Fig. 4.—Portions of the pars plana of the ciliary body in high magnification, showing details of the inflammatory process in the region of the pigmented and nonpigmented epithelium. In *A*, a patch of granulation tissue contains fibroblasts and capillaries predominantly. In *B*, there is the more extreme disorganization of the pigmented epithelium, and pigmented epithelioid nodules are conspicuous. Giant cells are present in both fields. The "nonpigmented" ciliary epithelium contains a considerable amount of melanin.

although leucocytic infiltration and inflammatory edema were also prominent in the inner portion of the ciliary body. Migration of leucocytes through the ciliary epithelium into the zonular region was clearly indicated.

An interesting finding was the presence of a considerable degree of melanotic pigmentation in the "nonpigmented" ciliary epithelium (Fig. 4). This pigmentation varied in intensity from field to field, but at no point was it dense enough to obscure the cell nuclei.

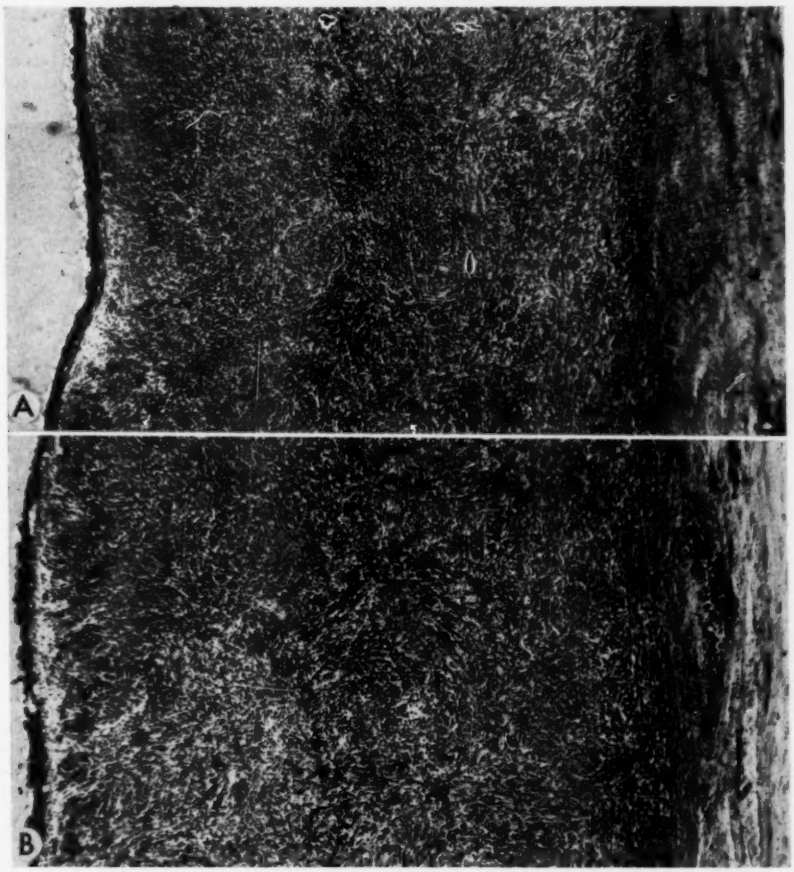

Fig. 5.—Two views of the choroid where the granulomatous architecture was extremely varied. In *A* epithelioid structures and leucocytic aggregations tend to be nodular; in *B* the appearance is more hodgepodge.

Choroid.—In the choroid there were rather massive infiltrations and proliferations in kaleidoscopic variety. For the most part, the choriocapillaris remained identifiable, but all other parts of the coat showed transformation into a more or less pigmented granuloma with a heavy plasma-cell and lymphocyte component (Fig. 5). There were scattered dense aggregations of epithelioid cells, resembling miliary or conglomerate tubercles (Fig. 6). Focally, giant macrophages were conspicuous. The lamina vitrea was thick and seemed to have func-

tioned as a confining membrane, preventing exudate and granulation tissue from advancing into the retina (Fig. 7*A*). In a zone just posterior to the ora serrata there was focal penetration of this lamina[7] (Fig. 3). Epithelioid nodules of the Dalén-Fuchs type were found protruding from the choroid into the retina at its periphery and in occasional sites in the fundus (Fig. 7*B*).

Sclera.—In and close to the emissaria of the sclera, where a lining of uveal tissue is normally present, extensions of the uveal inflammatory process were found. These were minimal exudative and granulomatous areas of involvement in continuity with those of the choroid (Fig. 5).

Retina.—Round-cell infiltration was found in the retina chiefly in the form of perivascular mantles of lymphocytes (Fig. 8). The optic-nerve entrance participated in this process, and

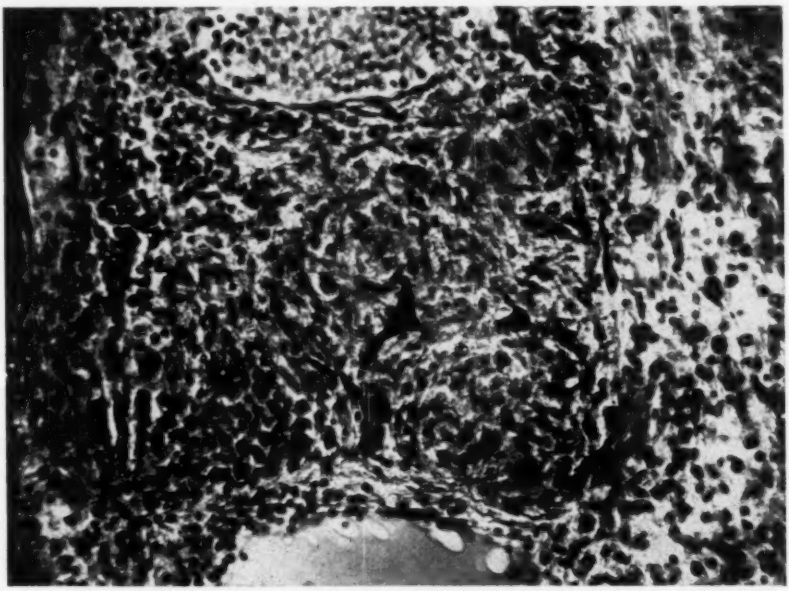

Fig. 6.—Two original choroidal vessels persisting. In the upper one there is "local leucocytosis." The epithelioid structure in the center resembles a conglomerate tubercle of tuberculosis but is pigmented and devoid of caseation necrosis. The leucocytic infiltration includes many plasma cells.

there was lymphocytic infiltration also in the pia-arachnoid. No epithelioid structures were found in these sites.

FURTHER OBSERVATIONS AND COMMENT ON SPECIAL FEATURES

Pigmentation and Necrosis.—The epithelioid cells and the overtly multinucleated giant cells in all parts of the uvea contained varying amounts of pigment. There

7. The fact that exudate and granulation-tissue structures commonly invade the very periphery of the retina in sympathetic ophthalmia, and in other conditions, and the ready passage of cells from the vascular layer of the pars plana of the ciliary body into and through the epithelial layers of the ciliary body suggest that in these regions the glassy membrane (lamina basalis) either is fenestrated or is easily interrupted in the course of inflammation.

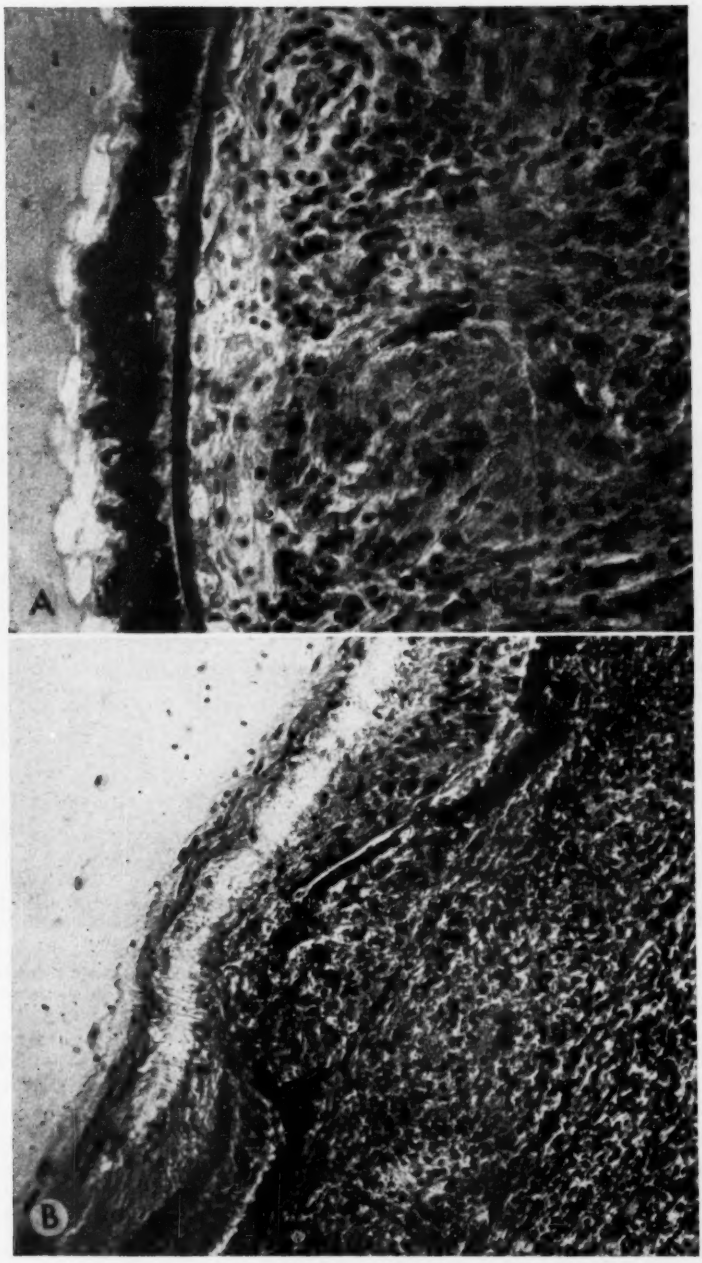

Fig. 7.—*A*, lamina vitrea intact and thickened. The inflammatory process is confined behind it. A relatively intact choriocapillaris persists. At this level the retina has been detached by albuminous fluid. The pigmented epithelium has become somewhat disorganized. A prominent plasma-cell component is evident in the choroid in the midst of proliferative changes.

B, Dalén-Fuchs nodule in the fundus. A granulomatous nodule has grown into the retinal structures, evidently through a break in the lamina vitrea. The pigmented epithelium has been partly elevated and partly disrupted by the process. The retina proper is thinned, disorganized, slightly elevated, and infiltrated.

were many other black masses, in which nuclei were invisible because of overabundance of melanin. This feature has been uniformly observed in studies of the exciting eye and is regarded by many as evidence that sensitization to ocular melanin is an etiologic factor in the condition. In the choroid the source of the pigment is obviously the chromatophores, and they, presumably, must die if their pigment is to be released. In the iris and the ciliary body pigment is made available to phagocytic cells not only by chromatophores but also by the pigmented epithelium in those structures. The marked ability of these epithelial cells to proliferate suggests that they may be the more important source of melanin. The degree of pigmentation acquired by epithelioid cells and giant cells may, therefore, be regarded in part as an index to the extent, and perhaps the rate of destruction, of pigment-

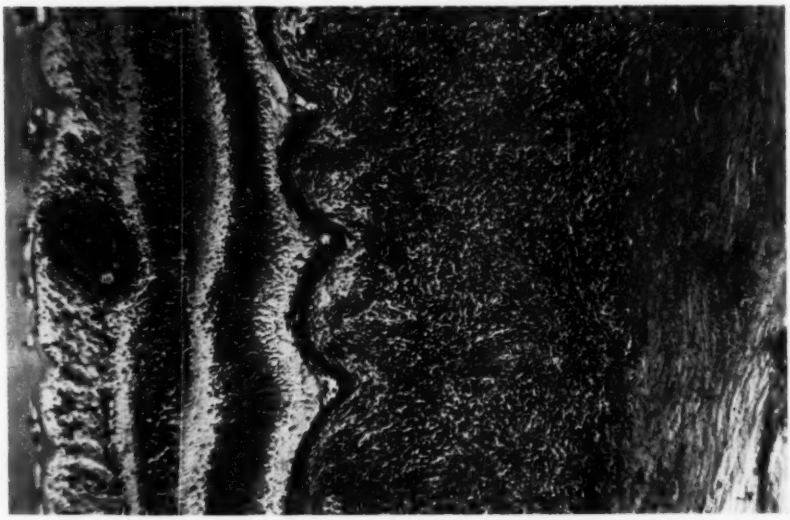

Fig. 8.—Confinement of the granulomatous inflammation behind the lamina vitrea, at a point where the retina has not been detached. Some extension into the sclera is seen. Lymphocytic infiltration in the retina is chiefly perivascular. These cells presumably have been furnished by the blood supply of the retina, and not by that of the choroid.

bearing or pigment-producing cells. In this connection it is of interest to observe that in at least two discrete foci, one in the iris and another in the ciliary body, there was frank necrosis involving the pigmented epithelium. In the ciliary site abundant granular pigment had been liberated, and here there was a most intense pigmentation of macrophages, some of which were enormous giant cells (Fig. 9*A*). A more sharply localized patch of necrosis on the posterior surface of the iris was bordered by a zone of granulomatous tissue (Fig. 9*B*).

The necrotic patches in both situations contained granular detritus that included a large amount of pigment. A bordering fringe of radially arranged black structures suggested the palisades of epithelioid cells found at the periphery of caseous portions of various granulomas. Were these not areas of caseation necrosis masked by pig-

mentation? The answer was sought by bleaching out the melanin and restaining sections containing necrotic foci. The resulting preparations, in which only a trace of pigment remained, showed central patches of coagulative necrosis with a considerable number of polymorphonuclear and other leucocytes in the midst of a cellular detritus. The "fringe" that had been obscured by pigment was now seen as a radially arranged, convoluted border of epithelioid structures (Fig. 10*A*). Without the melanin these patches appeared in no respect different from the caseous foci seen in granulomas of diverse origin. Formerly it has been believed that caseation necrosis does not occur in sympathetic ophthalmia, perhaps because the necrotic areas occasionally encountered have not been subjected to examination after bleaching.[8]

The presence of melanotic pigment within the "nonpigmented" ciliary epithelium has been noted above. This finding, to which I have not found previous reference, raises the question of the possibility of elaboration of melanin by these cells. Cells of identical embryologic derivation become the pigmented-epithelium layer of the iris. The alternative explanation is phagocytosis of the pigment, a property not usually manifested by the ciliary epithelium.

Components of the Granulation Tissue.—It has been noted that parts of the uvea showed chiefly exudative inflammation, but in most fields a type of productive (or proliferative) inflammation predominated. The latter, in simplest terminology, can be called granulation tissue, but since it formed a considerable mass (*ωμα*) of new tissue and had the peculiar features that characterize this disease entity, it would properly be described as the granuloma of sympathetic ophthalmia. Whereas the nonspecific forms of granulation tissue involve growth of capillaries and fibroblasts, and little else, this granuloma contained epithelioid cells in nodular, and other histic, arrangements and was pigmented. It was not possible to identify all the cells that contained pigment, but some at least were ordinary chromatophores originally present in the involved areas. Fibroblasts were not easily recognized because of the widespread pigmentation, but in many foci they were numerous (Fig. 4*A*). In most of the granulomatous areas vascularity was not conspicuous. Original

8. I do not believe that the finding of these patches of necrosis can be interpreted to indicate that this case is one of uveal tuberculosis, syphilis, or other known specific infection. That can hardly negate all the classic features of sympathetic ophthalmia present. On the other hand, it has been taught for more than half a century that caseation does not occur in this condition, a belief that cannot lightly be brushed aside. Among "special points of diagnostic importance," Duke-Elder (Text-Book of Ophthalmology, Vol. 3, St. Louis, C. V. Mosby Company, 1941, p. 2348) lists "the absence of tissue destruction, caseation and necrosis (sic)." Death of individual cells most certainly does occur, as in all inflammations, but necrosis is regularly absent from the small epithelioid nodules and is only occasionally found elsewhere. Samuels (Tr. Am. Ophth. Soc. **30**:253, 1932) remarked that "liquefaction that is sometimes seen in streaks in large masses of specific infiltration is not to be confounded with the caseation of tuberculosis." Meller (von Graefes Arch. Ophth. **89**:248, 1914), earlier, had pointed out that necrosis in this disease differs from the caseation of tuberculosis in that it occurs in streaks or channels among, and not in the center of, the collections of epithelioid cells. The necrotic foci I have described were not streaks. Perhaps the question is largely one of terminology. What is caseation other than a form of necrosis with "cheese-like" gross physical characteristics? Microscopically it presents many disparate appearances. With heavy pigmentation, it was quite beyond recognition in my case. The necrotic areas bordered by pigmented granulomatous tissue doubtless have immunologic significance, which would be lost if we were to continue to hand down the adage concerning a supposed invariable absence of caseation in sympathetic ophthalmia.

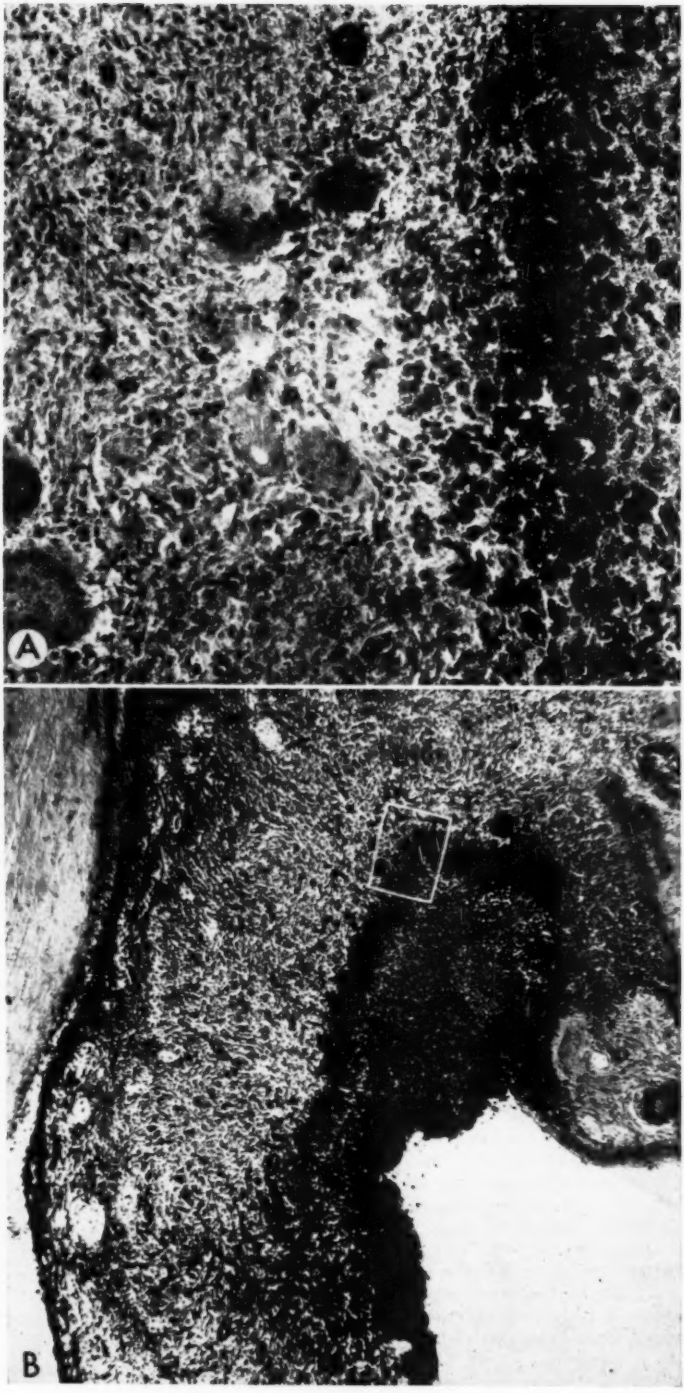

Figure 9

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vessels persisted in many fields, but the new-tissue proliferation had wiped out much of the normal vascular supply. Occasionally this process could be seen in progress (Fig. 10*B*). Although not richly vascular, the newly formed granuloma had a newly formed capillary vasculature of its own.

That exudation of fluid was an important part of this inflammatory disease was strikingly shown by swelling of the tissues, by detachments of uvea and retina, and by the presence of a coagulable, albuminous lymph in the aqueous and vitreous media. Leucocytes had accompanied this exudation of fluid and appeared in varying numbers throughout the tissue and in all the tissue spaces and chambers. For analytical purposes and for convenience of description, as customary, the processes detailed above have been considered as though more or less dissociated. Actually, each represented only an aspect of an over-all picture, the granulomatous inflammatory lesion of sympathetic ophthalmia in a particular sympathizing eye. In every essential respect this lesion was the same as that regularly found in the exciting eye.

PATHOLOGIC FEATURES ANTEDATING THE SYMPATHETIC INFLAMMATION

Such profound disease as that ascribed to the sympathetic ophthalmia must have tended to mask whatever had been abnormal in this eye prior to the onset of the specific disease process. It is important, however, to attempt to exclude from the pathognomonic part of the picture any antecedent, but unrelated, disturbances. An immature cataract was known to have been present prior to the operation on the other eye. The intumescent, cataractous character of the lens cannot properly be ascribed to the sympathetic inflammation, even though the process is known to produce cataract and may have augmented the changes in the lens in this instance. There was moderately advanced arteriosclerosis in all the tissues, consistent with the age of the patient. There was no evidence of severe vascular retinopathy, although the retina and choroid had been focally adherent. There was no evidence that glaucoma had been present prior to the sympathetic inflammation, but increased tension of recent development was indicated by clinical findings and by the recession of the lamina cribrosa and cupping of the optic disk. All the detachments were of recent occurrence. Lastly, it should be noted that there was no sign of any previous perforating or other injury, either surgical or accidental. It may be said, then, that the lesion of sympathetic ophthalmia was present in an almost "pure" state and, especially, without the direct results of injury that almost invariably complicate the picture as it is seen in the exciting eye.

SUMMARY AND CONCLUSIONS

The opportunity to investigate the lesion of sympathetic ophthalmia in an enucleated "sympathizing" eye presents itself very infrequently; few such examina-

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EXPLANATION OF FIGURE 9

Fig. 9.—*A*, margin of a patch of total necrosis in a fold of the ciliary body, along the right border of the field. A zone of jet-black macrophages borders the necrotic tissue, and many heavily pigmented, enormous giant cells are nearby.

B, patch of necrosis dipping into the tissue at the junction of the posterior surface of the iris and the anterior face of the ciliary body. The necrosis involves epithelial layers and underlying stroma and consists of a brown to black mass of granular detritus, devoid of visible nuclei. A dense, black fringe of pigmented (epithelioid?) cells and an outer, less pigmented, granulomatous portion form a wall about the necrotic focus. Except for the pigmentation, this structure suggests the radially arranged periphery of a partly caseous granuloma (see Fig. 10*A*).

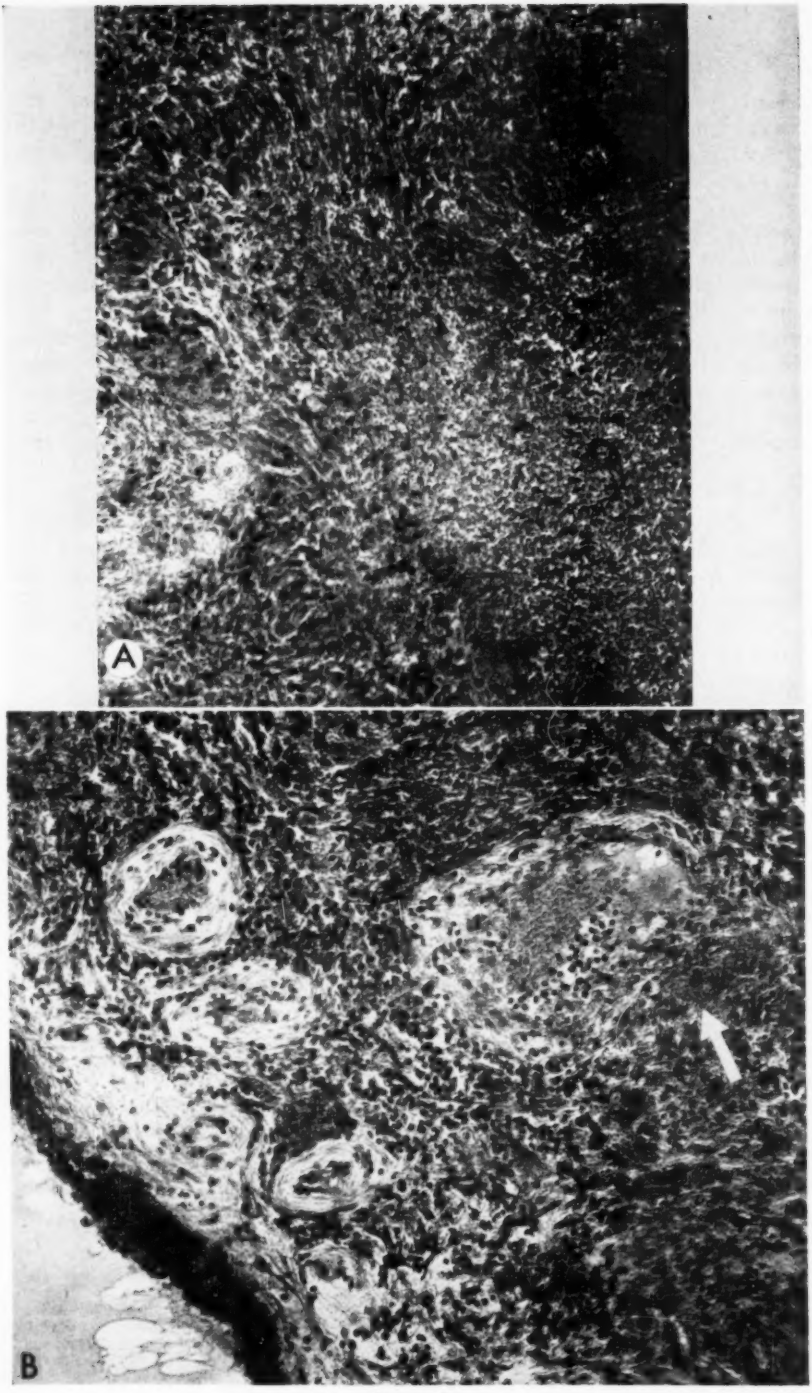

Figure 10

(See legend on opposite page)

tions have been reported in the British and European publications, and none, to my knowledge, has previously been recorded in the American literature.

An eye enucleated in a florid state of inflammation, 5 weeks after the onset of the involvement in that eye and 15 weeks after an extracapsular cataract extraction on the opposite eye, furnished the material for study of the anatomic lesion of sympathetic ophthalmia in a "sympathizing" eye free of significant antecedent or coexistent pathologic disturbances.

The pathologic changes found have been described and discussed as an inflammatory process in which exudative and proliferative features had combined to produce a granulomatous uveitis with profound redistribution of uveal and epithelial melanin, including pigment phagocytosis by epithelioid and giant cells. There were, in addition, extensive detachments of the retina and choroid, and retinitis and optic neuritis of mild nongranulomatous type. The disease had produced acute glaucoma and had probably augmented an already existent degenerative cataractous change in the lens. The entire inflammatory picture has been represented as an uncomplicated, or pure, lesion of sympathetic ophthalmia.

Of considerable interest was the finding of pigmented necrotic foci bordered by black cellular aggregations. When the melanin was bleached out, these areas were seen to be granulomatous foci with centers of coagulative necrosis. Although caseation necrosis has been said not to occur in sympathetic ophthalmia, in this instance there were two necrotic areas which when deprived of obscuring pigmentation appeared to be caseous portions of granulomatous structures. It is suggested that this observation be checked by examination of other eyes after bleaching; in fact, all ocular tissues masked by heavy pigmentation may advantageously be studied with the pigment removed or reduced in amount.

Pigmentation was discovered in the "nonpigmented" ciliary epithelium. This feature, to which I have found no previous reference, might be attributed to phagocytosis by the epithelial cells, or possibly to elaboration of pigment by these cells.

In general, the observations made in the study of this sympathizing eye emphasize the already well-established fact that the specific lesion of sympathetic ophthalmia is the same in the exciting eye and in the eye secondarily involved.

121 DeKalb Ave. 1.

EXPLANATION OF FIGURE 10

Fig. 10.—*A*, necrotic patch shown in Figure 9 *B* after the section had been bleached to reduce the melanotic pigmentation. What was seen as a black border now appears as a zone of granulomatous tissue, rich in epithelioid cells, arranged like a picket fence about the necrotic (caseous?) material. This field represents a high-power view of approximately the area outlined in white in Figure 9 *B*.

B, portion of the iris showing some of the original vasculature, which is sclerotic. The arrow indicates a point of invasion of a vessel by granulomatous tissue.

SURGERY OF OCULAR TRAUMA

Therapy of Secondary Intraocular Infection

IRVING H. LEOPOLD, M.D.
PHILADELPHIA

IN THIS antibiotic age one would expect the incidence of post-traumatic intraocular infection to be almost nil. Unfortunately, too many traumatized eyes have been lost because of intraocular infection. It is disheartening to see secondary infection develop within 24 hours after an otherwise uneventful, rapid extraction of an intraocular foreign body. This has occurred in spite of prophylactic and postoperative administration of antibiotics.

Within the past three months six cases of intraocular infection associated with penetrating foreign bodies have been encountered (Table 1).

Several noteworthy facts can be gleaned from these cases. In all of them penicillin or penicillin and streptomycin were given systemically before operation. The dose varied from 300,000 to 600,000 units of penicillin, injected intramuscularly. Streptomycin was administered in a dose of 0.5 to 1 gm. daily. In spite of such therapy, infection developed in all cases. This means either that the organism responsible was not sensitive to penicillin or streptomycin or that these agents were not reaching the infection-susceptible agent in sufficient concentrations. The latter possibility cannot be stressed too strongly. It has been shown by the experimental studies (von Sallmann and associates,[1] Struble and Bellows,[2] Leopold,[3] and Sorsby and Ungar[4]) that systemically administered penicillin fails to penetrate readily into the vitreous humor. Streptomycin likewise penetrates poorly into the intraocular fluids from the blood stream (Leopold and Nichols[5]). It is true that in the presence of infection these antibiotics penetrate more readily (Leopold and LaMotte[6]). However, in the usual doses these agents, when administered systemically, fail to

From Wills Hospital.

Presented at the Sectional Meeting of the American College of Surgeons, Atlantic City, N. J., Feb. 12, 1952.

1. von Sallmann, L.; Meyer, K., and Grandi, J.: Experimental Study on Penicillin Treatment of Ectogenous Infection of Vitreous, Arch. Ophth. **32**:179, 1944.

2. Struble, G. E., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, J. A. M. A. **115**:685, 1944.

3. Leopold, I. H.: Intravitreal Penetration of Penicillin and Penicillin Therapy of Infections of the Vitreous, Arch. Ophth. **33**:211, 1945.

4. Sorsby, A., and Ungar, J.: Control of Experimental Infection of the Vitreous by Penicillin, Brit. J. Ophth. **34**:645, 1950.

5. Leopold, I. H., and Nichols, A.: Intraocular Penetration of Streptomycin Following Systemic and Local Administration, Arch. Ophth. **35**:33, 1946.

6. Leopold, I. H., and LaMotte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal Inflamed and Abraded Corneas, Arch. Ophth. **33**:43, 1945.

TABLE 1.—*Penetrating Foreign Bodies and Intraocular Infection*

Patient	Age	Foreign Body	Time of Onset of Infection	Culture Studies	Therapy Prior to Appearance of Infection	Therapy of Infection	End-Result
A. H.	18	Magnet extraction through pars planum	24 hr. after extraction	Aqueous and vitreous sterile	Systemic therapy Penicillin, 300,000 units every 12 hr. Cortisone, 200 mg. in 24 hr. Streptomycin, 0.5 gm. every 12 hr.	Intravitreal penicillin and streptomycin Systemic penicillin, 300,000 units every 4 hr. Streptomycin, 0.5 gm. every 6 hr. Subconjunctival penicillin and streptomycin	Phthisis bulbi in 1 mo.
P. Z.	36	Magnet extraction through pars planum	Panophthalmitis prior to extraction, evident 24 hr. after injury	Aqueous and vitreous sterile F. B.	Systemic penicillin, 300,000 units daily Cortisone, 100 mg. daily	First 36 hr.: Intravitreal chloramphenicol, 250 γ/0.1 cc. Systemic chloramphenicol, 3 gm. stat.; 1 gm. every 6 hr. Second 36 hr.: Penicillin, 1,000,000 units subconjunctivally Streptomycin, 50,000 γ subconjunctivally Terramycin, 5 mg./cc. by iontophoresis and 250 γ/0.3 cc. subconjunctivally	Eye quiet; light perception
I. T.	36	Magnet extraction through pars planum	Panophthalmitis 24 hr. after extraction	Aqueous and vitreous sterile	Systemic penicillin, 300,000 units daily Streptomycin, 0.5 gm. daily	Penicillin, 300,000 units 4 times daily Streptomycin, 0.5 gm. 2 times daily Penicillin, 1,000,000 units and streptomycin, 50,000 γ subconjunctivally	Evisceration
D. F.	30	Forceps extraction of protruding nail	36 hr. after extraction	Aqueous and vitreous sterile	Cortisone, 300 mg. in 24 hr. Penicillin, 300,000 units daily	Terramycin, 250 γ intravitreally Terramycin, 250 γ subconjunctivally Terramycin, orally, 1 gm. stat. and 0.5 gm. every 4 hr.	Evisceration
C. M.	18	Magnet extraction through pars planum	24 hr. after extraction	B. subtilis from aqueous and vitreous	Cortisone, 300 mg. Penicillin, 300,000 units every 4 hr. Streptomycin, 0.5 gm. every 6 hr.	Penicillin, 600,000 units every 4 hr. Streptomycin, 0.5 gm. every 6 hr. Sulfadiazine, 1 gm. every 4 hr.	Evisceration
G. D.	26	Glass; forceps extraction of extruding edge through ciliary body	24 hr. after extraction	Aqueous sterile	Penicillin, 300,000 units once daily	Sulfadiazine, 1 gm. every 4 hr. Penicillin, 600,000 units every 4 hr.	6/12

control experimental vitreous infections. Only when massive doses are administered systemically can the experimental vitreous infections be influenced even slightly (von Sallmann and associates,[1] Leopold,[3] and Sorsby [7]). Experimentally, one can control intraocular infections best with locally administered antibiotics (von Sallmann,[1] Leopold,[3] and Sorsby [7]). From these experimental studies, it is evident also that the earlier therapy is instituted, the better are the results. Dunnington and von Sallmann,[8] Rycroft,[9] Zorab,[10] and Sorsby [7] have demonstrated these observations in clinical cases.

These six tabulated cases are illustrative of many of these important, and apparently overlooked, points. It is evident that although the foreign body was removed without any difficulty in a number of these cases, secondary infection developed within 24 hours in spite of continued systemic administration of penicillin and/or streptomycin. The amount of penicillin and/or streptomycin administered was inadequate. The dosage schedule employed, although satisfactory for infections elsewhere in the body, is not satisfactory for production of adequate intraocular levels of penicillin. The results also indicate that intraocular infections once established are difficult to control and that cultures of the intraocular fluids in these cases are usually sterile and are not helpful in detecting the cause of the infection or in selecting the antibiotic. It is evident from these cases that penicillin in the form previously administered will not prevent the development of postoperative intraocular infection. It is also apparent that once the infection has developed subconjunctival injections of penicillin in the order of 1,000,000 units, along with streptomycin, 50,000 units, will not control intraocular infection in all cases, nor will systemic or intravitreal administration of chloramphenicol (chloromycetin®) or systemic, intravitreal, or subconjunctival administration of terramycin. One eye showed some temporary improvement after the intravitreal injection of penicillin and streptomycin, followed by subconjunctival injection of penicillin and streptomycin and systemic administration of massive doses of penicillin and streptomycin. The only successful case was one in which the eye responded to massive doses of sulfadiazine and penicillin administered systemically.

Armed with these clinical and experimental data, one can outline a therapy schedule likely to succeed. Treatment of intraocular infections following ocular trauma, i. e., penetrating wounds, penetrating foreign bodies, intraocular surgery, etc., can be divided into prophylactic therapy and therapy of existing infections.

PROPHYLACTIC THERAPY

An antibiotic should be used prior to the surgical procedure, whether it is to be extraction of a foreign body or a cataract, or repair of a ruptured globe. In this way one can establish a concentration of the antibiotic in the blood stream and in the ocular fluids prior to opening the eye. It has been shown that paracentesis or

7. Sorsby, A.: Penicillin, in Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1947, Vol. 2, Chap. 34, p. 394.

8. Dunnington, J. H., and von Sallmann, L.: Penicillin Therapy in Ophthalmology, Arch. Ophth. **32**:353, 1944.

9. Rycroft, B. W.: Penicillin and the Control of Deep Intra-Ocular Infections, Brit. J. Ophth. **29**:57, 1945; Sub-Conjunctival Penicillin and Intra-Ocular Infection, ibid. **29**:501, 1945.

10. Zorab, E. C.: War Surgery of the Eye in Forward Areas, Brit. J. Ophth. **29**:579, 1945.

surgical opening of the eye increases the permeability of the blood-aqueous barrier and facilitates the intraocular penetration of all antibiotics from the blood stream.

In the selection of an antibiotic for this purpose, it must be realized that penicillin alone is not adequate, as it will hinder the growth only of Gram-positive agents. The combination of penicillin and streptomycin will give a broader antibacterial spectrum. However, both these agents penetrate the blood-aqueous barrier poorly. It is quite possible that, because of inadequate dosage, an otherwise susceptible organism might produce a severe secondary intraocular infection. Terramycin and aureomycin have broad antibacterial spectra but penetrate poorly into the ocular fluids and tissues. Therefore, they, like the penicillin-streptomycin combination, are not entirely satisfactory. Chloramphenicol and sulfonamides penetrate into the ocular tissues and fluids of the normal eye decidedly better than penicillin, streptomycin, aureomycin, and terramycin. Chloramphenicol is a more efficient antibacterial agent than the sulfonamides for most organisms. It would seem advis-

TABLE 2.—*Schedule of Prophylactic Antibiotic Therapy of Penetrating Ocular Wounds*

Agent	Dosage	Time of Administration, Hr. Preoperative	Time of Administration, Hr. Postoperative
Chloramphenicol (recommended first choice)	Initial: 3 gm. orally Maintenance: 1 gm. every 6 hr.	3	36
Penicillin*	Initial: 1,000,000 units I. M. or I. V. Maintenance: 1,000,000 units every 8 hr.	1	.. 48
Streptomycin	Initial: 2 gm. I. M. or I. V. Maintenance: 1 gm. every 8 hr.	1	.. 48
Terramycin or aureomycin (third choice because of poor intraocular penetration)	Initial: 1 gm. orally Maintenance: 1 gm. every 6 hr.	3	.. 36

* Probenecid (benemid®), 2 gm. orally with initial dose of penicillin; 0.5 gm. every 6 hr. for maintenance.

able, therefore, to use this agent prophylactically in eyes that have sustained ocular trauma. The dose recommended on the basis of penetration studies (Leopold, Nichols, and Vogel [11]; Leopold [12]) would be 3 gm. of chloramphenicol initially and 1 gm. every six hours. Therapy should be started several hours before any attempt at ocular surgery if possible. This allows time for an adequate blood level and ocular-fluid concentration to be achieved. If the blood concentration is high at the time the eyeball is opened, more of the antibiotic can spill into the intraocular structures (Table 2).

If for some reason the recommended prophylactic therapy of first choice cannot be used, one may then employ the penicillin-streptomycin combination. These drugs can be administered intramuscularly or intravenously. The latter method affords

11. Leopold, I. H.; Nichols, A. C., and Vogel, A.: Penetration of Chloramphenicol U. S. P. (Chloromycetin®) into the Eye, Arch. Ophth. **44**:22, 1950.

12. Leopold, I. H.: Clinical Trial with Chloramphenicol in Ocular Infections, A. M. A. Arch. Ophth. **45**:44, 1951.

the higher intraocular concentrations. Simultaneously administered probenecid (benemid®) will prolong the penicillin concentrations. The time interval for administration of maintenance doses may be every four to eight hours. It may be necessary only to administer these massive doses at less frequent intervals (Marshall [13]), but for security the more frequent injection schedules are advisable for the present.

THERAPY OF ACTUAL INFECTION

Unfortunately, in spite of strict surgical techniques, and even programs such as those outlined above, intraocular infection will occur. In the past infections have developed because of inadequate administration techniques, allowing subeffective concentrations to come into contact with susceptible organisms. Infections will continue to occur when respectable concentrations of an antibiotic have been obtained but organisms are not susceptible.

Experimental and clinical studies (von Sallmann and associates,[1] Leopold,[3] Rycroft,[9] Sorsby and Ungar [4]) have shown that established vitreal infections do not respond well to systemically administered penicillin, even in massive doses. Leopold, Wiley, and Dennis [14] have shown that the same negative results occur with systemic use of streptomycin. Direct vitreal injection of penicillin (Weizenblatt,[14a] von Sallmann,[1] Leopold,[3] and Sorsby [7]) and streptomycin (Leopold and associates [14] and Shoemaker [15]) arrested severe infections of the vitreous. Massive subconjunctival injections are also successful (Sorsby and Ungar [4]). In addition, all these studies have demonstrated that in dealing with vitreal infections adequate treatment must be instituted as early as possible in order to have any chance of success.

SELECTION OF ANTIBIOTIC

Clinically, one is able only exceptionally to select an antibiotic by culture or smear studies. Therapy must be instituted immediately, before there is time for bacteriologic analysis. Even when culture studies have been employed, they are often discouraging and disappointingly negative. Cultures of material from the cul-de-sac and of the aqueous and vitreous are remarkably sterile in many of the eyes although frank enophthalmitis or panophthalmitis exists. Therefore, one must choose an antibiotic or antibiotic combination with a wide antibacterial spectrum and use a method of administration that insures high intraocular concentrations. The schedule indicated in Table 3 is suggested.

Initial systemic administrations of penicillin and streptomycin should be made intravenously when possible. This will produce the highest blood concentrations and therefore the greatest spill-over into the intraocular fluids and tissues. If these measures fail to produce any clinical benefit in 24 hours, change to another antibiotic is imperative. Tolerated concentrations for intraocular injection of each of the antibiotics listed in Table 3 have been determined for the experimental animal

13. Marshall, A. K.: The Dosage Schedule of Chemotherapeutic Agents, Pharmacol. Rev. **4**:85, 1952.

14. Leopold, I. H.; Wiley, M., and Dennis, R.: Vitreous Infections and Streptomycin: Experimental Studies, Am. J. Ophth. **30**:1345, 1947.

14a. Weizenblatt, S.: Penicillin in Treatment of Acute Endophthalmitis: Report of Case, Arch. Ophth. **36**:736, 1946.

15. Shoemaker, R.: Intravitreal Use of Streptomycin, Arch. Ophth. **41**:629, 1949.

eye (Leopold,[16] Vogel and associates,[17] and Cannon and associates [18]). On the basis of these studies, the concentrations indicated in Table 3 can be employed.

Subconjunctival injections of antibiotic agents other than penicillin and streptomycin or chloramphenicol can be used, but terramycin and aureomycin do not penetrate well from subconjunctival depots in low dosage. Data are not available at present on the results of massive subconjunctival injections with these agents. However, they produce extreme discomfort even when low doses have been injected subconjunctivally (deRoetth,[19] Bellows and associates,[20] and Cannon and associates [18]).

Chloramphenicol penetrates readily from the blood stream; so it can be utilized by the systemic (oral) route in the concentrations suggested for prophylactic therapy. With such an agent intravitreal or subconjunctival injection may not add significantly to its effectiveness. Sulfonamides likewise penetrate readily and can

TABLE 3.—*Therapy of Intraocular Infection*

Agent	Method of Therapy	Antibiotic	Dosage	Frequency
Penicillin-Streptomycin Combination*	Subconjunctival injection	Penicillin + streptomycin	1,000,000 units/ml. of 1:1,000 epinephrine or water 100,000 γ/ml. of 1:1,000 epinephrine or water	Repeat daily for 2 days
	Intravitreal injection	Penicillin + streptomycin	(If overwhelming infection) 5,000 units/0.05 ml. 1,000 units/0.05 ml., followed by subconjunctival injection, as above	Once
	Systemic therapy	Penicillin† Streptomycin	(Also give same drugs systemically) 1,000,000 units, initially, I.V. 1,000,000 units, I.M. 1 gm., initially, I.V. 1 gm., I.M.	Every 6 hr. Every 8 hr.
Chloramphenicol‡	Systemic therapy	Chloramphenicol	3 gm. stat. 1 gm.	Every 6 hr.
Other Antibiotics	Intravitreal injection	Aureomycin or terramycin	50 γ/0.1 cc. 250 γ/0.1 cc.	Once
		Bacitracin and/or polymyxin or neomycin	100 γ0.1 cc. 250 γ 250 γ/0.1 cc.	
	Systemic therapy		Additionally same drugs may be used systemically in massive doses	

* Therapy to be instituted if prophylactic chloramphenicol therapy has been unsuccessful.
† Probenecid (benemid®), 2 gm. orally with initial dose of penicillin; 0.5 gm. every 6 hr. for maintenance.
‡ To be used if prophylactic penicillin and streptomycin therapy have been unsuccessful.

be administered orally. It is important to start with a high initial dose, such as 3 gm., with each of the latter agents and continue with 1 gm. every four to six hours. The orally administered compounds may occasionally induce nausea. This action is undesirable after intraocular surgical procedures. Chloramphenicol is less annoying in this regard than terramycin and aureomycin.

16. Leopold, I. H.: Pharmacology and Toxicology [Annual Reviews], A. M. A. Arch. Ophth. **46**:159, 1951.

17. Vogel, A. W.; Leopold, I. H., and Nichols, A.: Neomyc[illegible] Ocular-Tissue Tolerance and Penetration When Locally Applied in the Rabbit Eye, Am. J. Ophth. **34**:1357, 1951.

18. Cannon, E. J.; Nichols, A. C., and Leopold, I. H.: Studies on the Intraocular Penetration and Toxicity of Terramycin, A. M. A. Arch. Ophth. **47**:344, 1952.

19. deRoetth, A., Jr.: Penetration of Aureomycin into the Eye, Arch. Ophth. **42**:365, 1949.

20. Bellows, J.; Richardson, V. M., and Farmer, C. J.: Aureomycin in Ophthalmology, Am. J. Ophth. **33**:273, 1950.

ROLE OF CORTISONE IN CONTROL OF INTRAOCULAR INFECTION

In four of the cases included in Table 4, cortisone, 100 mg. every eight hours or once daily, was given systemically after operation, in an attempt to reduce the traumatic uveitis. It is evident from the results in other cases, as reported by Thorpe,[21] Purnell and Leopold,[22] and others, that systemic and local administration of cortisone will reduce the severity of uveitis following trauma or intraocular surgery, without interfering significantly with wound healing. On the other hand, there are actions of cortisone which may be undesirable in the management of intraocular infections. It has been shown that cortisone does not alter the permeability of the normal eye (Leopold and associates,[23] Cook and MacDonald[24]) but that it will reduce the increased permeability of the blood-aqueous barrier following ocular inflammation (Cook and MacDonald[24]). If penicillin penetrates poorly into the normal eye and slightly better into the inflamed eye, indicating the increase in

TABLE 4.—*Intraocular Infection After Cataract Extraction*

Patient	Age, Yr.	Time of Onset of Infection	Culture Studies	Therapy Prior to Appearance of Infection	Therapy of Infection	End-Result
B. B.	75	24 hr. after extracapsular extraction	Aqueous, Ps. aeruginosa	Penicillin, 300,000 units once a day	Penicillin, 1,000,000 units subconjunctivally once daily Polymyxin, 250 mg./0.2 cc. into anterior chamber Terramycin, 0.5 gm. every 6 hr. intramuscularly	Evisceration
A. F.	55	24 hr. after extracapsular extraction	Aqueous, sterile	Penicillin, 300,000 units once daily Streptomycin, 0.5 gm.	Chloramphenicol, 3 gm. stat.; 0.5 gm. every 6 hr.	6/15
W. H.	60	24 hr. after extracapsular extraction	No cultures	None	Chloramphenicol, 3 gm. stat.; 0.5 gm. every 6 hr.	6/20
P. K.	68	24 hr. after intracapsular extraction	Aqueous, sterile	Penicillin, 300,000 units once daily Streptomycin, 0.5 gm. once daily	Penicillin, 1,000,000 units; 0.5 cc. once daily for 3 days Streptomycin, 50,000 units; 0.5 cc. once daily for 3 days	Evisceration
E. L.	71	24 hr. after intracapsular extraction	Aqueous, sterile	Penicillin, 300,000 units once daily Streptomycin, 0.5 gm. once daily	Terramycin, 250 mg./0.2 cc. into anterior chamber Penicillin, 1,000,000 units; 0.5 cc. subconjunctivally once daily for 2 days Streptomycin, 50,000 units; 0.5 cc. subconjunctivally once daily for 2 days	6/15

permeability associated with the inflammation, and cortisone blocks the increase in permeability produced by inflammation, cortisone will, therefore, decrease the penetration of penicillin into the inflamed eye. This indicates that in cases of potential infection one should avoid the use of cortisone until one is certain that no infection will develop, or one should not use antibiotics that depend for their intraocular concentration on the increased permeability associated with trauma or inflammation. These agents will probably be reduced in their intraocular penetration by the use

21. Thorpe, H. E.: Corticotropin (ACTH) and Cortisone in Ocular Surgery, Tr. Sect. Ophth. A. M. A., 1951, p. 159.

22. Purnell, J. E., and Leopold, I. H.: Cortisone in Ocular Disease: Further Studies, Am. J. Ophth. **35**:663, 1952.

23. Leopold, I. H.; Purnell, J. E.; Cannon, E. J.; Steinmetz, C. G., and McDonald, P. R.: Local and Systemic Cortisone in Ocular Disease, Am. J. Ophth. **34**:361, 1951.

24. Cook, C., and MacDonald, R. K.: Effect of Cortisone on the Permeability of the Blood-Aqueous Barrier to Fluorescein, Brit. J. Ophth. **35**:730, 1951.

of cortisone. Agents such as chloramphenicol and sulfonamides, which penetrate into the intraocular tissues of the normal eye, will not be greatly influenced by the use of cortisone. In recent studies, however, McDonald, Leopold, Vogel, and Mulberger [25] have been unable to demonstrate any significant reduction in the penetrability of streptomycin in severely inflamed eyes following administration of cortisone or hydrocortisone (Compound F).

COMMENT

It is discouraging to realize how difficult it is to control intraocular infections. In spite of the availability of many excellent antibiotics, eyes are still lost because of intraocular infection. Strict attention must be paid, therefore, to the many factors concerned that may lead to better control of this situation. One must be certain that an antibiotic is used prior to the development of infection. The best chance of therapy of intraocular infections is to prevent the infection from occurring initially, or from developing into a fulminating one. The chances of controlling a fulminating intraocular infection are extremely small. One should use an antibiotic which penetrates well into the intraocular fluids and structures. The antibiotic should have a wide antibacterial spectrum. At present the agents which answer these two criteria are chloramphenicol and the sulfonamides. Chloramphenicol is a more effective antibacterial agent than the sulfonamides and therefore should be given preference. It can be administered orally. This is usually an advantage. However, in a postoperative patient who has had a general anesthesia chloramphenicol will have to be administered parenterally, instead of orally. Parenteral preparations for such administration are available. There are many organisms which do not respond readily to chloramphenicol. If an infection develops in spite of the preoperative and postoperative administration of this drug, one must then change to the regimen suggested above, namely, subconjunctival and systemic administration of penicillin and streptomycin in massive doses.

Because of the difficulty of securing material for culture and of obtaining growth on cultures from this material, one will have to be guided by clinical response to the chosen antibiotic. If an eye does not respond within 24 hours, another antibiotic should be employed, particularly if the eye is losing ground. One may criticize the rapid change from one antibiotic to another on the grounds that certain antibiotics interfere with one another in their action against particular strains of organisms. However, there is no choice. If an eye is not responding to one antibiotic, one must either find a more successful antibiotic for that particular case or give in to the infection. Direct intravitreal injections of an antibiotic must be utilized in certain cases, particularly when there has been no response to subconjunctival injections of massive doses of the penicillin-streptomycin combination, and when there has been no response to adequate systemic doses of chloramphenicol and sulfonamides. One must not, however, exceed the dosage schedules which have been determined by virtue of experimental studies for intravitreal injection. Areas of choroiditis and vitreous disturbance will be noted at the sites of the intravitreal injections with each of these antibiotics.

It must be realized that intraocular infections, particularly after the otherwise uneventful extraction of intraocular foreign bodies in repair of penetrating ocular

25. McDonald, P. R.; Leopold, I. H.; Vogel, A. W., and Mulberger, R.: Compound F in Ophthalmology, presented at the Fourth Wills Hospital Conference, March 22, 1952.

wounds, are still an important cause of visual loss. Many questions have still to be answered in dealing with this problem. An outstanding problem is the lack of an explanation for the great number of sterile cultures obtained in the presence of clinical evidence of overwhelming intraocular infection. Perhaps this occurrence indicates a cause other than secondary infection for the purulent reaction after foreign-body extraction. However, until this is established, one must assume that an infection is responsible and treat accordingly.

Anterior-segment infections can usually be controlled by the methods available, whether it be by subconjunctival injection, by iontophoresis, by massive systemic dosage, by use of cotton packs, or by direct injection into the anterior segment.

Intraocular infections after cataract extraction appear to respond better to therapy than those resulting from penetrating foreign bodies (Dunnington and von Sallmann [8]). In Table 4 are listed five cases of intraocular infection following cataract extraction, in three of which the infection responded to therapy. It is easier to treat posterior-segment infections when the iris-lens barrier has been opened by extraction of the lens. There is definite evidence of the block provided by this barrier to the posterior movement of antibiotics and other substances when applied by iontophoresis, subconjunctival injection, or direct anterior-chamber injection (Adler,[26] Leopold,[3] von Sallmann [27]).

SUMMARY

In an effort to prevent the great visual loss due to secondary infections following the extraction of foreign bodies, it is recommended that adequate dosage schedules with the chosen antibiotic be employed before as well as after operation. On the basis of intraocular-penetration studies, chloramphenicol (chloromycetin®) would appear to be superior to the other antibiotics for systemic administration. Prophylactic failures in the past can be attributed to inadequate dosage, to the possibility of antibiotics being used which did not have a wide antibacterial spectrum, and possibly to the use of cortisone, which may have blocked the intraocular penetration of systemically administered antibiotics. Once secondary infection has developed after the extraction of a foreign body, vigorous therapy must be instituted, either by subconjunctival and systemic administration of massive doses of a combination of penicillin and streptomycin, or by systemic use of massive doses of chloramphenicol or direct intravitreal injection of the various antibiotics in tolerated doses. There is little time to be lost. If an antibiotic appears to be unsuccessful in controlling the infection after a 24-hour period, another antibiotic should be tried. In dealing with intraocular infections, one cannot be guided by culture studies, because of the time involved and because of the difficulty of obtaining positive cultures.

26. Adler, F. H.: Investigation of Sugar Content of Ocular Fluids Under Normal and Abnormal Conditions, and Glycolytic Activity of Tissues of Eye, Tr. Am. Ophth. Soc. **28**:307, 1930.

27. von Sallmann, L.: Controversial Points in Penicillin Therapy of Ocular Diseases, Arch. Ophth. **39**:752, 1948.

Clinical Notes, New Instruments and Techniques

PHENYLEPHRINE (NEO-SYNEPHRINE®) OINTMENT

A Superior Preparation

ROBERT H. BEDROSSIAN, M.D.
DREXEL HILL, PA.
AND
JOHN W. DEICHLER, M.D.
PHILADELPHIA

PHENYLEPHRINE (neo-synephrine®) hydrochloride was first described as a therapeutic agent in ophthalmology by Heath in 1936.[1] The more recent literature has suggested additional uses for this drug.[2] More widespread and frequent use of phenylephrine has been somewhat limited by the unsatisfactory preparations now on the market. All too frequently the ophthalmologist wishes to use the solution or emulsion, only to find that the contents of his bottle have turned a dirty brown. He also hears patients complain vigorously about the severe stinging that occurs, even though he has previously instilled a topical anesthetic.

NEW PREPARATION

To meet these objections, a preparation of 10% phenylephrine (neo-synephrine®) hydrochloride in a 0.75% methylcellulose base was made for one of us (J. W. D.).[3] This drug comes in an ointment tube, is crystal clear, has a mildly gelatinous consistency, and comes out of the tube as a drop, rather than the ribbon of the usual ointment bases. This preparation produces only a mildly unpleasant sensation when instilled in the eye and requires no anesthesia prior to its use. We have preparations that have been opened for over six months and have found that they have remained clear, do not increase the irritation experienced by the patient, and have suffered no loss of potency.

Since the effects of phenylephrine are well known, we have evaluated this new and more satisfactory preparation on a clinical basis.

Systemic Effect of Topical Instillation.—A drop of 10% phenylephrine hydrochloride ointment was instilled in the lower cul-de-sac of each eye in 20 patients with normal blood pressure and 20 patients with hypertension. Their pulse rates and blood pressures were taken before and 15 to 30 minutes after the instillation. There was no significant effect on either the pulse rate or the blood pressure. None of the patients experienced any stimulatory sensations.

Effect on Ocular Tension.—Fifteen nonglaucomatous patients had tonometer readings prior to and every 15 minutes for two hours after the instillation of the phenylephrine ointment. There was no increase in the tension in any of the 30 eyes. This drug was also used in the eyes of 10 glaucomatous patients five minutes prior to the instillation of diisopropyl fluorophosphate. The usual temporary increase in tension that occurs with the use of the latter drug did not occur.

Comparison with 10% Phenylephrine Hydrochloride Emulsion.—As a control, 1 drop of 10% phenylephrine hydrochloride emulsion was instilled in the right

1. Heath, P.: Neo-Synephrine Hydrochloride: Some Uses and Effects in Ophthalmology, Arch. Ophth. **16**:839-846 (Nov.) 1936.

2. Heath, P., and Geiter, C. W.: Use of Phenylephrine Hydrochloride (Neo-Synephrine HCl) in Ophthalmology, Arch. Ophth. **41**:172-177 (Feb.) 1949.

3. Prepared by Winthrop-Stearns Inc., New York.

eye of 50 patients, and, for comparison, a drop of the phenylephrine hydrochloride ointment was placed in the left eye of the same patients. Fifteen premature and newborn infants were included in this group. Pupillary sizes were compared at the end of one-half, one, two, and four hours. As was expected, there was little complaint when the ointment was instilled, but bitter objection was voiced when the emulsion was used. Maximum dilation of the pupils usually occurred between one-half and one hour. In only three patients was there a difference in pupillary size of more than 2 mm. at the end of one-half or one hour. In these three patients the eye with the larger pupil was the one in which the ointment was instilled. The duration of mydriasis in all patients was approximately the same for the control and the test eyes. In only three of the adults was maximum mydriasis less than 7 mm. in the eyes in which the phenylephrine ointment was instilled. Mydriasis lasted at least three hours in most cases. The pupils usually began to react at about three hours, even though dilated.

In 15 infants both preparations were somewhat less effective, as mydriasis usually lasted between one and two hours. In three infants the pupils did not dilate to more than 5 mm.

Clinical Effect.—We have tried phenylephrine ointment in over 100 patients. Many attempts were made to dilate pupils with posterior synechiae by using the phenylephrine ointment. When this was ineffective, subconjunctival injections of atropine and epinephrine usually failed also. In a few cases, three installations of the phenylephrine ointment produced dilation of pupils that did not dilate with the subconjunctival injections.

CONCLUSIONS

Phenylephrine (neo-synephrine®) hydrochloride ointment (10% phenylephrine hydrochloride in 0.75% methylcellulose) is as potent a mydriatic as the other topical preparations of 10% phenylephrine hydrochloride. This new ointment preparation does not have the severely irritative effect on the eye, nor does it deteriorate as do the older preparations now available.

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AN IODINE-VAPOR APPLICATOR FOR TREATMENT OF DENDRITIC KERATITIS

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SOME POSSIBLE advantage in convenience over the well-known "iodine-scrub" treatment for dendritic or herpetic keratitis is offered by a simple modification which I have made and have utilized in treating approximately 40 patients with this type of keratitis during the past eight years. The initial impression has been obtained that the modified treatment is as good as the old, and in some cases possibly better, but the data are as yet insufficient for a significant comparison of effectiveness. The modification consists in substituting for the usual swabbing with tincture of iodine an exposure of the virus-infected cornea to a controlled dose of iodine vapor from a tube containing iodine crystals, with no rubbing or scrubbing or subsequent "neutralization." The element of convenience lies in the fact that the application of iodine vapor to the cornea is easily made in a few minutes with the patient in a sitting position.

An impression that the iodine-vapor procedure constitutes reasonably satisfactory treatment was obtained from the observation that in only six cases did dendritic keratitis fail to heal after a single application. In most cases the keratitis was healed in three to four days, and in those few cases in which ulceration persisted after a single treatment a more successful result usually followed a second application. In none of the cases in which treatment was given in the typical dendritic stage has metaherpetic or disciform keratitis developed. In five cases an impression of some superiority of the iodine-vapor treatment was obtained from the observation that healing followed this form of treatment when applications of tincture of iodine had been unsuccessful. In three of these cases there was deep involvement of the cornea, with only indistinct remains of a dendritic pattern. Gray stromal edema extended from front to back of the cornea, with no dense or opaque infiltrates, but with a small yellowish deposit at the back of the cornea in the center of the keratitic area. The posterior surface of the cornea in the involved area was in folds, and there were a flare and cells in the aqueous. The belief that these severe, deep, and protracted corneal disturbances were caused by herpes simplex was based on a history of antecedent attacks of dendritic keratitis. In all cases iodine scrubbing had previously been used, without apparent benefit. After a single iodine-vapor application there were progressive healing of the cornea and whitening of the eye, but with considerable residual corneal scarring. This improvement following iodine-vapor treatment may, of course, have been fortuitous.

The iodine-vapor applicator, which is good for years of repeated use, may be prepared from a small glass-stoppered test tube, as illustrated in Figure 1, manufactured by the Corning Glass Works and designated by them as the No. 5640 One-Millimeter Volumetric Flask. Better still is a glass-stoppered tube, illustrated in Figure 2, which may be fabricated by a glass blower from standard parts so constructed that the glass stopper is on the outside, covering and protecting the end of the applicator tube when it is not in use. This arrangement obviously has the advantage of preventing bacterial contamination of the end of the tube which is to be in contact with the cornea. In fact, the end of the tube is automatically kept sterilized by being

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continuously surrounded by saturated iodine vapor when not in use.[1] Two sizes of the preferred type of tube are shown in Figure 2. The smaller tube, which the manufacturer designates as Size 14/20, is suitable for all except the most extensive corneal involvement. The larger tube, Size 19/22, will cover the whole cornea but is infrequently required. The applicator portion of either type of tube is filled with iodine crystals to approximately 20 mm. from the open end. The crystals are held in place by means of a small wad of fiberglas® (Owens-Corning Fiberglas Corporation, Basic Fiber No. 28). Iodine vapor sublimes from the crystals readily at room temperature and passes through the fiberglas® to the open end of the tube, which during treatment is held in contact with the cornea and at other times is kept closed with the glass stopper to prevent loss of iodine.

Fig. 1.—Iodine-vapor applicator of simple form.

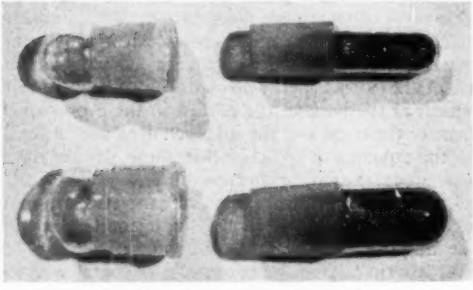

Fig. 2.—Iodine-vapor applicators of preferred form.

Treatment is performed with the patient sitting upright in a chair, with the back of the head resting against a wall or other support. The cornea to be treated is anesthetized with 4 or 5 drops of 0.5% tetracaine hydrochloride (pontocaine® hydrochloride). One drop of the same anesthetic is also applied to the other eye to facilitate suppression of blinking. The patient is requested to maintain fixation of gaze upon some object across the room horizontal with the eyes in order to keep the eyes still and in proper position during treatment. The lids of the eye to be treated are held apart by the ophthalmologist with the thumb and forefinger of one hand, while the open end of the iodine-applicator tube is held lightly in contact with

1. The parts from which this tube is constructed are manufactured by the Corning Glass Works, Corning, N. Y., under the name No. 6600 Ground Joint.

the cornea in such a manner that it is centered over the ulcer and the tube is essentially horizontal, as illustrated in Figure 3. The duration of application is dependent upon the distance from the surface of the iodine crystals to the corneal surface. With a crystal-to-cornea distance of 16 to 20 mm. an effective dose is delivered in 3.5 minutes. The dose delivered is determined by the time of application, provided the temperature of the tube is always approximately the same, usually a little above room temperature from the warmth of the fingers holding it, and provided the stopper has been removed only just before application to the cornea. After each use of the applicator any moisture on the open end of the tube should be wiped off with cotton before the tube is stoppered and put away.

Immediately after the treatment a light gray-brown disc, approximately 8 mm. in diameter, is seen on the surface of the cornea corresponding to the area exposed. Grayness from epithelial edema gradually becomes more pronounced, particularly along the borders of the dendritic figure, usually making the ulcer itself more conspicuous. No additional local treatment is required. The exposed epithelium spontaneously sloughs off and usually within 48 hours is replaced by a thin layer of new

Fig. 3.—Manner of exposing the cornea to iodine vapor for treatment of dendritic keratitis.

epithelium. Until the epithelium is regenerated, there is generally much discomfort. It has seemed better not to employ any local anesthetic during this period but to depend upon closure and immobilization of the eyes plus systemic use of codeine and acetylsalicylic acid. In some cases in which there have been repeated previous dendritic ulcers, with consequent marked hypesthesia of the cornea, little discomfort has been experienced from the treatment and no closure of the eye or medication has been necessary. It has been the impression of patients who have at different times undergone both the usual iodine-scrub treatment and the present iodine-vapor treatment that the amount of discomfort from the two procedures is approximately the same.

The clarity of the cornea after iodine-vapor treatment in cases of early dendritic keratitis ordinarily returns practically to normal. Recurrences of dendritic keratitis months and years after successful iodine-vapor treatment have been several, and there is no reason to think that the present treatment differs in any way from iodine scrubbing with respect to the incidence of these late recurrences.

243 Charles St., 14.

Annual Reviews

GLAUCOMA

A Review of the Literature 1951-1952

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A LARGE number of publications dealing with glaucoma continues to appear each year. These papers emphasize the intriguing, as well as the serious, nature of the disease, which remains one of the major causes of blindness in the world. The many ideas as to the origin of glaucoma indicate that the cause and likewise the remedy remain obscure.

Sugar's [1] book, published during the past year, has brought the subject up-to-date and has consolidated many of the current ideas on the subject. Although his presentation is largely from the gonioscopic, or mechanical, point of view, other approaches are discussed. In the preface of his book he emphasizes the changing nature of our knowledge of glaucoma.

PRIMARY GLAUCOMA

A. Mechanism

The arguments between those of the neurovascular school of origin and those who accept the gonioscopic classification, the "mechanical school of origin," continue unabated, although some of the differences seem in the process of being resolved. Grant's [2] careful work, which will be discussed later, has contributed a mass of objective evidence which points to the obstructive nature of glaucoma. Although his findings are best explained by concepts previously established by gonioscopy, they can also be interpreted from the neurovascular point of view on the basis of Thomassen's work, in which he suggested that increased venous pressure might cause the elevated ocular tension in glaucoma. Until the differences between the neurovascular and the gonioscopic approach are resolved, it seems advisable, as in previous years, to separate papers on the nature of glaucoma into these two broad categories for purposes of this review.

1. *Neurovascular School.*—The neurovascular school of origin of glaucoma assumes that the disease results from an abnormality in the ocular circulation, which might occur on a local basis within the eye or as a consequence of a disturbance in the general circulatory system of the body as a whole. Because the entire neurovascular concept is somewhat nebulous, it is difficult to be specific about the exact mechanism. Contributing factors include disorders of the hypothalamic region, the autonomic nervous system, and the endocrine system. Papers dealing with various phases are therefore considered under their own headings as nearly as possible.

(*a*) Circulatory Disturbances Within the Eye: The leading proponent of the neurovascular school of origin of glaucoma is Sir Stewart Duke-Elder. In a recent Proctor lecture [3] at the University of California, he neatly summarized many of the arguments in support of the neurovascular school, based largely on the work which is being conducted at Moorfields Hospital, in London, by such observers as Langley, Miller, MacDonald, Thomassen, Leydhecker, Swanljung, and himself.

One phase of their investigations dealt with diurnal variations in tension in normal and in glaucomatous eyes, which they believe result from a habitual hypothalamic rhythm imposed upon the organism by long-standing environmental con-

1. Sugar, H. S.: The Glaucomas, St. Louis, C. V. Mosby Company, 1951.

2. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **46**:113, 1951.

3. Duke-Elder, S.: Phasic Variations in Ocular Tensions in Primary Glaucoma, Am. J. Ophth. **35**:1, 1952.

ditions. Duke-Elder compares this diurnal variation in tension with diurnal variations in temperature, sleep, and diuresis. The pattern of all these functions persists unchanged for some time even if the person's sleep habits are reversed, although it does reverse after a long-term change in habits. That they are probably fundamental is indicated by the presence of diurnal rhythms of temperature in newborn infants. Certain characteristics of the diurnal-tension curve further suggests its fundamental nature. Duke-Elder states that it shows an identical rhythm in the two eyes of the same subjects. The curve does not depend upon bodily posture, activity, osmotic changes, pupillary size, action of light upon the ocular capillaries, or massage of fluid out of the eye by muscular movements during the day.

Duke-Elder admits that this concept of the diurnal-tension curve is somewhat hypothetical, but he believes that at least it indicates a regulating mechanism that tends to maintain intraocular pressure at a physiological level within a slight rhythmic variation in spite of the stresses and strains of life. In glaucoma, the variations are much more pronounced because for some reason the glaucomatous eye has lost its normal power of control and, as a result, the rhythmic changes in pressure run riot in a gross and uncompensated swing of pressure.

Duke-Elder, on the basis of the work of Langley and Swanljung,[4] describes the following three types of diurnal-tension curves in chronic simple glaucoma: (1) the falling type, in which the tension is highest in the morning, occurring in 20% of eyes; (2) the rising type, in which the tension is low in the morning and climbs during the day, occurring in 25% of eyes, and (3) the double-variation type, in which there is a double variation in the daily curve, found in 55% of eyes. In all types there is a tendency, which persists until early moring, for the tension to fall in the early evening, after 6 p.m. He believes that this instability of ocular tension is much more indicative of glaucoma than the recording of a high tension and that it explains the low-tension glaucoma in which the tension is always within normal limits but abnormal diurnal variations occur. That these curves are due to an underlying circulatory instability, Duke-Elder believes, is supported by their characteristic configuration and the fact that abnormal patterns of the oscillations persist, although at a lower level, after normalization of tension by surgical means. In his opinion, only an underlying circulatory instability could explain such behavior. Such arguments are difficult to refute.

Duke-Elder divides the evolution of narrow-angle glaucoma into three stages. In the first, the tension is generally normal and only occasionally rises toward the end of the day, usually after worry, stress and strain, or a visit to the movies. He states that similar rises in tension, as a rule, can be elicited in such eyes by the darkroom test. This phase may last for years, or an acute congestive attack may supervene. He emphasizes that iridectomy may control the disease in these eyes permanently, even though physiological and gonioscopic tests show that no permanent artificial channels of drainage have been established.

Adherents to the gonioscopic school would immediately rebut these arguments by stating that such rises in ocular tension are characteristic of iris block of the trabeculum and are not related to the diurnal-tension curve. The angles of all these

4. Langley, D., and Swanljung, H.: Ocular Tension in Glaucoma Simplex, Brit. J. Ophth. **35**:445, 1951.

eyes are extremely narrow. The increased tension results from periods of closure of the angle, whether it be due to provocative mydriasis tests or the stress and strain of everyday life. The dark-room test is probably dependent upon the mechanical factor of mydriasis, while emotional strain and worry introduce a neurovascular element. The mechanism by which closure of the angle occurs is discussed elsewhere (page 761 [5]). Peripheral iridectomy prevents such a rise in tension by producing a new channel for the direct flow of aqueous from the posterior to the anterior chamber. No alteration in the neurovascular reflexes needs be assumed.

In the second stage of development of congestive glaucoma, Duke-Elder states that unusual events are not required to excite marked variations in tension. The phasic variations, according to Duke-Elder, are different from those in simple glaucoma. On the whole, they tend to reach their peak in the evening and then fall during sleep, almost inevitably to normal or subnormal levels.

Advocates of the mechanical school would state that fulminating attacks were narrowly being averted in such eyes, that the tension characteristically rises in the evening, during the hours of dusk, and that the tension falls to normal during sleep, at least partially, as a result of pupillary constriction. It is well known that acute attacks of glaucoma can be terminated by the induction of sleep. Whether this can be wholly attributed to miosis, to diminution of nervous tension, or to a diurnal variation in tension due to some fundamental bodily mechanism is difficult to determine. However, most of the available objective evidence supports a miotic effect.

Duke-Elder suggests three ways in which the fundamental mechanism might exert its effect upon the eye to cause the rhythmic variations in tension which he found characteristic of glaucoma: (1) a periodic variation in the formation of intraocular fluid, (2) a variation in the ease of its drainage, and (3) a disturbance in the vascular circulation. Assuming that the intraocular fluid is formed by a secretory mechanism superimposed upon a process of diffusion, the rises could be said to result either from a periodic increase in secretory activity or from increased diffusion, due to increased permeability of the ocular capillaries. On the basis of the work of Langley and MacDonald,[6] who showed that the concentration of fluorescein in the aqueous remains very high for a long time during periods of rising tension, but that the concentration falls very rapidly during periods of falling tension, they believe that an impediment to outflow of aqueous is the best explanation. Although not mentioned, Grant's [2] work seems even more indicative of such a mechanism.

Duke-Elder indicates that the obstruction has to be functional rather than organic to explain the phasic diurnal variations in glaucoma. He found it difficult to imagine an impediment which is effective at 12 o'clock and ineffective at 2 o'clock of the same day. He objects, for this reason, to any explanation which assumes the presence of organic or mechanical obstruction. He therefore suggests that the obstruction is somewhere in the trabeculum-canal of Schlemm mechanism or its exit chambers. Both he and Thomassen and Bakken [7] believe that it is related to the venous pressure.

5. Haas, J., and Scheie, H. G.: Peripheral Iridectomy in Narrow Angle Glaucoma, Tr. Am. Acad. Ophth., to be published.

6. Langley, D., and MacDonald, R. K., cited by Duke-Elder.[3]

7. Thomassen, T. L., and Bakken, K.: Anatomical Investigations into the Exit Canals of Aqueous Humour: A Preliminary Report, Acta ophth. **29**:257, 1951.

His argument is not insurmountable, because even though the obstructive element in glaucoma remained constant and the outflow of aqueous likewise was constant, the ocular tension could vary if the rate of formation of aqueous increased or decreased. There seems less reason to assume a variability in the rate of escape of aqueous than in the rate of formation.

Aqueous formation is influenced profoundly by capillary permeability. Duke-Elder himself believes that marked instability of the ocular capillary network is indicated by the bulbar pressure test. External pressure upon the eye causes little fall in tension in glaucomatous eyes and a more pronounced fall in normal eyes. This is followed by a significant abrupt rise in tension in glaucomatous eyes and by little rise in normal eyes. He believes that this reactive rise indicates capillary instability.

The rise in ocular tension might also be explained on an obstructive basis by assuming that external pressure was followed in all eyes by an increased flow of aqueous. If outflow was retarded, as in glaucoma, the tension would rise, but in normal eyes outflow channels might be sufficient to avert it. Duke-Elder further holds that it is a capillary phenomenon because glaucomatous eyes responded in their characteristic way to this test only during phases of rising tension. Also, the results of such tests as the water-drinking test, which depends upon osmotic changes in the blood, are unaffected by the diurnal variation, being positive with equal frequency in the ascending and in the descending phase.

It is of interest that Duke-Elder explains the effect of miotics on a neurovascular basis. He believes that miotics cause a fall in the venous pressure in the exit veins from the eye, increase the permeability of the ocular capillaries, and accelerate drainage of aqueous, owing to a relative fall in pressure of the resilient veins. He is of the opinion that it is not due to contracture of the pupil and opening of the angle except in certain cases of narrow-angle glaucoma. He concludes that these drugs minimize the phasic variations in tension preventing the rises in tension in glaucoma by dilating the ocular capillaries, opening up the capillary circulation, and lowering the pressure in the exit veins.

Duke-Elder concludes by reiterating that glaucoma is due to lack of the local vascular control which normally keeps variations of tension within comparatively strict limits. This instability consists of two elements. One is on the venous side and explains the obstructive element in glaucoma. The other is a capillary instability. He believes that, in spite of normalization of tension by miotics or surgical means, the prognosis for glaucoma may be bad because the underlying vascular disease persists and may lead to deterioration of the eye and visual function.

Poos [8] also incriminates the ocular venous system. He suggests that blood flow through the vortex veins, which is governed at least partially by orbital venous pressure, might be the important factor in glaucoma. His theory is rather complex and thus far speculative. Serr [9] objects very strenuously to it and states that he

8. Poos, F.: Vortex-Sinus Function and the Minute Volume: Therapy of Circulation of the Globe, von Graefes Arch. Ophth. **151**:275, 1951.

9. Serr, H.: Most Important Physical and Physiologic Bases of a New Theory on Intraocular Pressure and Glaucoma, Proposed by F. Poos, von Graefes Arch. Ophth. **151**:581, 1951.

believes the fault to lie on the arterial side. Niedermeier [10] believes that a local disturbance in the autonomic regulating mechanism of the choroid may be at fault, particularly in the parasympathetically controlled "choroidal pillow."

(*b*) Relation of Glaucoma to Systemic Neurovascular Disease: This year, as in the past, articles have appeared linking glaucoma with systemic vascular diseases. Such correlations are difficult because the incidence of glaucoma is highest in the last decades of life, a time when the incidence of systemic vascular disease also increases. Bedrossian [11] reports a patient who had glaucoma associated with a mediastinal tumor of sufficient size to cause serious interference with venous return. The veins of the neck and those of the anterior chest wall were conspicuously engorged. The eyelids and arms were swollen. The venous pressure was recorded at 310 mm. water. Blood return through all the venous exit channels of the eye was therefore impeded. Bedrossian suggests that pilocarpine must have controlled the ocular tension through its effect upon the circulatory system. One might object that there is no way of knowing whether or not the patient might not have had glaucoma prior to onset of his mediastinal tumor. The paper, however, is interesting in view of Thomassen's work suggesting that glaucoma might be associated with increased venous pressure.

Keeney and Leopold [12] conducted a careful evaluation of capillary function in 50 patients with primary glaucoma as compared with capillary function in 50 patients of the same age group and sex distribution who did not have glaucoma. They found that there was no increase in capillary fragility and no change in the morphology of the capillary loops of the fingernail beds or in the number of capillary loops per given area in the forearm. They did find that there was a statistically significant increase in capillary filtration, as indicated by lymph-flow measurements in their patients with glaucoma as compared with those for the control group. Lloyd [13] made skin biopsies on patients with chronic simple glaucoma and found histologic evidence of edema in a significant number of those with moderately or extremely high ocular tension.

(*c*) Factors Underlying Neurovascular Instability: (1) Disturbances in the parasympathetic nervous system: Bottino [14] found the serum-cholinesterase activity to be higher at night, during prolonged darkness, than under conditions of illumination and suggests that this may be a factor in glaucoma, particularly in view of the diurnal-tension curve. Rumyantseva [15] believes that in the first phase of acute glaucoma sympathicotonia, in the form of angiospasm of the blood vessels of the eye, is associated with increased pressure, pain, and dilatations of the pupil. In the

10. Niedermeier, S.: Vasomotor Phenomena and Glaucoma, von Graefes Arch. Ophth. **151**:551, 1951.

11. Bedrossian, E. H.: Increased Intraocular Pressure Secondary to Mediastinal Syndrome, A. M. A. Arch. Ophth. **47**:641, 1952.

12. Keeney, A. H., and Leopold, I. H.: Evaluation of Capillary Mechanisms in Primary Glaucoma, A. M. A. Arch. Ophth. **47**:720, 1952.

13. Lloyd, J. P. F.: Skin Biopsy in Chronic Glaucoma, Tr. Ophth. Soc. U. Kingdom **71**:215, 1951.

14. Bottino, C.: Influence of Illumination and of the Day-Night Rhythm on Serum Cholinesterase in Man. Ann. ottal. e clin. ocul. **77**:174, 1951.

15. Rumyantseva, A. F.: Pathogenesis of Primary Inflammatory Glaucoma, Vestnik oftal. **30**:8, 1951.

second stage, a disturbance in the parasympathetic system comes into play, first with paresis, and then with paralysis, of the ciliary nerves. Outflow of fluid from the eye is blocked, and the high intraocular pressure remains stationary. Of patients with various types of glaucoma 40% were found on observation to have elevated blood pressure, along with instability of the autonomic nervous system. There seems little authoritative basis for accepting such lines of thought, although it is well known that parasympathomimetic drugs lower elevated intraocular pressure.

(2) Glaucoma and the sympathetic nervous system: The sympathetic nervous system has been incriminated by many writers, who follow lines of reasoning somewhat similar to those used in implicating the parasympathetic system. Courtis and Nunez [16] agree with Duke-Elder that primary glaucoma is due to a neurovascular instability but point particularly to the sympathetic supply to the eye. Dienstbier and Balik [17] compare a group of glaucomatous patients with a group of patients with normal eyes by injecting effective doses of tetraethylammonium chloride intravenously in 15 patients with glaucoma; they were unable to find any correlation between glaucoma and systemic sympathicotonia or vagotonia. Although systemic effects were obtained with this autonomic-ganglion-blocking agent, they found no prominent changes in intraocular pressure. They conclude, therefore, that the central vegetative nervous system is not the decisive factor in glaucoma. They could not, of course, exclude the possibility of local ocular disturbances in either of these two systems.

(3) Disturbances of the blood-aqueous barrier: Ansler and Huber [18] devised a fluorescein test for study of the blood-aqueous barrier, which consisted of injecting fluorescein sodium intravenously and then measuring and following the concentration in the anterior chamber by dimming the slit-lamp beam until the greenish tint of the fluorescein was no longer visible. The brightness of the beam was then determined in terms of the amperage of the light source. They found that eyes with glaucoma showed no significant alteration in permeability of the blood-aqueous barrier. Miller and Swanljung [19] used the same method and found that eyes with both congestive and chronic simple glaucoma showed normal ranges of permeability. After topical administration of pilocarpine and physostigmine, fluorescein entered the eye more readily.

(4) Hypothalamic region: Many observers have suggested the hypothalamic region as the site of the disturbance in primary glaucoma. Magitot has long favored the theory of such an origin of glaucoma, and he has many followers, particularly on the Continent. Support is given to this theory by the well-known relationship of emotional disturbance to increased intraocular pressure. These authors note

16. Courtis, B., and Nunez, R. B.: Theory of Pathogenesis of Primary Glaucoma, Arch. oftal, Buenos Aires **26**:26, 1951.

17. Dienstbier, E., and Balik, J. I.: Autonomical Balance in Patients with Glaucoma Examined by Means of the K/Ca Quotient, Ceskoslov. oftal. **7**:395, 1951; Attempt to Eliminate the Influence of the Central Nervous System in Glaucoma, ibid. **7**:163, 1951.

18. Ansler, M., and Huber, A.: Technique and Principles of the Fluorescein Test, Ophthalmologica **121**:130, 1951.

19. Miller, S. J. H., and Swanljung, H.: Appearance of Fluorescein in the Aqueous of Glaucomatous Eyes, Brit. J. Ophth. **35**:356, 1951.

definite fluctuations in intraocular pressure with emotional reactions. Weinstein [20] agrees with Schmerl and Steinberg [21] that acute glaucoma is related to a disturbance in the hypophyseal region. He believes that the rationale for the dark-room test was based on a strictly neurovascular disturbance rather than on pupillary dilatation. Kluzer and Matteucci [22] lent further support to this theory when they found that the ocular tension was decreased after prefrontal lobotomy. One would immediately ask why the incidence of glaucoma in psychopathic patients was not much higher. Del Rio Cabanas [23] reports a case of acute glaucoma following a head injury. He believes that this resulted from instability of the neurovegetative response on the part of the eye, which permitted glaucoma to occur.

(5) Glaucoma and the cochleovestibular apparatus: Cristini and Cristini, in 1950, noted a relationship between the vestibular apparatus and glaucoma. The similarity of the physiology of endolymph to that of the intraocular fluid was mentioned, and it was suggested that the same neurovegetative factor might cause an increase of pressure in the two fluids. This year, Bottino [24] and Ferraris de Gaspare and Maffei [25] report similar observations. The latter authors found that patients with chronic simple glaucoma showed diminished audiometric and labyrinthine responses as compared with those of a control group. They even suggest that this observation might serve as the basis of a new provocative test for glaucoma.

(*d*) Low-Tension Glaucoma and the Neurovascular Theory: Low-tension glaucoma offers one of the best arguments in favor of the neurovascular theory of the origin of glaucoma. For many years the entity of optic atrophy with cupping of the head of the optic nerve and visual-field defects characteristic of glaucoma occurring without elevated ocular tension has been known. Whether this symptom complex is truly glaucoma, or whether it results from a separate disease of the optic nerve, has never been determined. Weekers [26] states that any of the three cardinal symptoms of glaucoma (ocular hypertension, visual-field defects, and cupping of the nerve head) may occur independently of the others to form incomplete glaucoma. Weekers limits the diagnosis of low-tension glaucoma to those eyes in which the tension does not exceed 25 mm. Hg Schiøtz. He is of the opinion that even exhaustive studies might not reveal any abnormality of diurnal variations in tension. He adds the observation that ocular-rigidity studies show normal values. Langley and Swanljung,[4] in a careful study of 24-hour tension curves of 34 patients, express the opinion that fluctuations in tension (variations in the diurnal tension) are of much greater importance and yield more information than do provocative

20. Weinstein, P.: Clinical Data Concerning the Central Origin of Glaucomatous Attacks, Orvosi hetil. **92**:1233, 1951.

21. Schmerl, E., and Steinberg, B.: Neurovascular Mechanism and the Control of Intraocular Pressure, Am. J. Ophth. **35**:469, 1952.

22. Kluzer, G., and Matteucci, P.: Present Views on Primary Glaucoma: Critical Considerations on Central Regulation of Intraocular Pressure, Rass. ital. ottal. **20**:83, 1951.

23. del Rio Cabanas, J. L.: Traumatic Glaucoma, Arch. Soc. oftal. hispano-am. **11**:1064, 1951.

24. Bottino, C.: Simultaneous Attack of Congestive Glaucoma and Acute Deafness; Report of Case, Ann. ottal. e clin. ocul. **77**:132, 1951.

25. Ferraris de Gaspare, P. F., and Maffei, G.: Use of Audiometric Studies as Provocative Test in Diagnosis of Chronic Simple Glaucoma, Riv. oto-neuro-oftal. **26**:294, 1951.

26. Weekers, R.: Corneal Rigidity in Cases of Glaucoma Without Ocular Hypertension, Ophthalmologica **122**:187, 1951.

tests. They believe that any variation of 10 mm. Hg or more should be regarded as indication of glaucoma regardless of tension level, and that a difference of 4 mm. Hg between two eyes of the same patient is a preglaucomatous sign. Duke-Elder's [3] recent views have already been discussed.

Advocates of the mechanical school, however, believe that true low-tension glaucoma, if an entity, is extremely rare. Most patients suspected of having low-tension glaucoma, if carefully studied, will show an organic cause for deterioration of the optic nerve, such as syphilitic involvement or pituitary tumor. Stajduhar,[27] in an excellent paper, states that optic-nerve deterioration may occur through direct damage to the nerve fibers by sclerotic vessels or by obstruction of small nutritional blood vessels to the optic nerve, which result in degenerative foci. He mentions still another possibility, namely, that if the pressure in the eye is considerably greater than the cerebrospinal fluid pressure the nerve head might become excavated, a hypothesis advocated by Klar. Forni [28] reports a case of osteitis deformans (Paget's disease) in which low-tension glaucoma was suspected, but x-ray examination of the skull revealed deformity of the optic foramina due to Paget's disease. He recommended x-ray studies of the skull and optic foramina in any case in which glaucoma is simulated in the presence of normal ocular tension. This practice should be universal.

2. *Mechanical School.*—(*a*) Miscellaneous Articles in Support of the Mechanical Theory: The mechanical theory of the origin of glaucoma, based upon concepts established largely by gonioscopy, is becoming increasingly accepted in this country. Much support has been given to that point of view by Grant's excellent work in tonography. His original article was briefly reviewed in the annual review of glaucoma for 1950-1951.[29] Using an electronic Schiøtz tonometer equipped with a recording galvanometer, he was able to measure both the rate of formation of aqueous humor and the rate of its escape from the eye. His technique presented a means of determining whether or not alterations of steady-state intraocular pressure are due to changes in resistance to outflow or to changes in rate of aqueous-humor formation.

In his most recent paper, Grant [2] reports observations on 600 human eyes, the majority of which had glaucoma. He had first made inflow and outflow determinations on a group of normal eyes. By comparison with the values for these eyes, a heterogeneous group of glaucomatous eqes showed a depression of the rate of outflow of aqueous. He found no instance in which glaucoma could be attributed to increased formation of aqueous.

When the eyes were classified under acute (narrow-angle) and chronic simple (wide-angle) types, he found that during the acute phases of narrow-angle glaucoma marked obstruction to aqueous outflow occurred. After normalization of tension by miotics, the aqueous outflow became normal except in instances in which bands of peripheral anterior synechia had formed. Thirteen fellow eyes of the eyes with acute narrow-angle glaucoma were examined gonioscopically and found to have extremely narrow, but open, angles. In these eyes, the rate of aqueous outflow and

27. Stajduhar, J.: Etiology of Pseudoglaucoma, Ophthalmologica **122**:129, 1951.

28. Forni, S.: Paget's Disease and Pseudoglaucoma, Confinia neurol. **11**:20, 1951.

29. Scheie, H. G.: Glaucoma: A Review of the Literature 1950-1951, A. M. A. Arch. Ophth. **46**:677, 1951.

the intraocular pressure were normal. In at least one of these eyes the rate of outflow of aqueous was measured and found to be normal prior to an attack. A short time later, during an attack of acute congestive glaucoma, the rate of aqueous outflow had become greatly reduced, but after normalization of tension by carbachol drops the outflow returned to normal.

These observations, by Grant, in cases of narrow-angle glaucoma offer strong support to concepts previously established by gonioscopy. It is believed by advocates of the gonioscopic school that the underlying cause of the disease is narrowness of the angle of the anterior chamber. The eye is otherwise normal and the trabeculum-canal of Schlemm mechanism is thought to function normally. The tension does not become elevated unless the iris root, for some reason, comes into contact with the trabeculum. These conclusions coincide beautifully with Grant's demonstration of normal outflow of aqueous during the interval between attacks, when the aqueous has access to the trabeculum, and of marked reduction in outflow during the acute attack, when the trabeculum is blocked by the iris root.

In eyes with narrow angles there are probably several secondary, or so-called angle-crowding, factors which allow closure of the angle and precipitate an acute attack. It is well known that pupillary dilatation allows the iris, through relaxation of the sphincter, to come into contact with the trabeculum in such eyes. The importance of the neurovascular element is indicated by sudden rises in tension, which follow emotional upsets or minor trauma to the eye. It seems possible that they might cause an increase in the rate of flow of aqueous, with ballooning forward of the iris periphery until it comes into contact with the corneoscleral wall. Such a mechanism would necessitate assuming a physiological iris bombé, due to resistance to aqueous flow from the posterior to the anterior chamber. The site of resistance might be the area where the iris rests upon the lens. Such reasoning is supported by the observations of Haas and Scheie,[5] who noted marked deepening of the angle of the anterior chamber, which resulted from settling backward of the iris after peripheral iridectomy. They believe that the iris bombé had been eliminated by the iridectomy, which provided a direct route of flow of aqueous from the posterior to the anterior chamber. Banziger, in 1922, had previously suggested that the aqueous compressed the iris root against the trabeculum in acute glaucoma, although he did not specify how it occurred. Chandler,[30] in his excellent article on narrow-angle glaucoma, accepted the hypothesis of physiological iris bombé and confirmed the deepening of the angle of the anterior chamber following peripheral iridectomy.

If a physiological iris bombé were present, it should become accentuated by pupillary dilatation, because relaxation of the iris sphincter would likewise relax the midportion and root of the iris, which could then more readily be carried forward against the trabeculum, as apparently does occur during mydriasis tests. Likewise, any increase in aqueous flow, whether on an emotional or other basis, might cause a slight pushing forward of the iris to make contact with the trabeculum, where it would be held much like a lace curtain when carried forward against a screen by even a gentle flow of air.

Grant's tonographic studies on eyes with primary wide-angle glaucoma indicating an obstructive mechanism have now been accepted by at least some advocates of both the gonioscopic and the neurovascular school. The site and nature of the

30. Chandler, P. A.: Narrow-Angle Glaucoma, A. M. A. Arch. Ophth. **47**:695, 1952.

obstruction can only be speculated upon at present. It could be due to organic changes in the trabeculum, the canal of Schlemm, or the aqueous veins. On the other hand, it could be on the basis of a neurovascular disturbance which impedes flow through the aqueous veins, as suggested by Thomassen [7] and Duke-Elder. This seems to be the common meeting ground of the two schools and, in my opinion, underscores the vulnerability of the neurovascular school, which, although it now accepts the obstructive nature of glaucoma, must assume that the cause is neurovascular, whereas the gonioscopic school can accept any plausible explanation, including a neurovascular involvement obstructing the aqueous veins.

The greatest objection to the gonioscopic classification has resulted from poor terminology. Eyes with so-called wide-angle glaucoma do not necessarily have wide-open angles. A better term would have been "open-angle" glaucoma, because no specific angle depth need be assumed. All that is implied is that aqueous always has access to the trabeculum-canal of Schlemm mechanism and that the angle is not closed. The depth, therefore, can vary from wide-open to very narrow, but as long as the aqueous does have access to the trabeculum the course of the disease is that of chronic simple glaucoma. When the angle is very narrow, however, there is no reason that an iris block might not occur and acute congestive glaucoma be superimposed, just as it is believed that acute glaucoma occurs in healthy eyes, but possessing a narrow angle, which makes them vulnerable. Pupils in such eyes must not be dilated, but one can use mydriatics with no danger of acute glaucoma even in eyes with chronic simple glaucoma if the angles are wide-open. While the angle depth may vary greatly in simple glaucoma (wide-angle glaucoma), in my experience 100% of the patients with acute glaucoma have narrow angles which appear closed during congestive attacks.

Grant's work is being confirmed by others. Prijot and Weekers [31] and Weekers and Prijot [32] confirmed the work of Grant on tonographic studies of 66 eyes with chronic simple glaucoma. They, too, found that the rate of fluid expulsion was much lower than in normal eyes, an observation which points to resistance to aqueous outflow. They concluded that the resistance was a very real one because the greatest obstruction occurred in the eyes with the highest ocular tension.

Wortham [33] was able to produce a mechanical type of glaucoma experimentally by placing plastic discs in the pupillary aperture in the anterior chamber. A pupillary block resulted which caused iris bombé and acute glaucoma, lasting about 72 hours and disappearing spontaneously as the iris became separated from the disc. This observation, incidentally, offered further evidence in support of Leber's theories regarding flow of aqueous from the posterior to the anterior chamber.

(*b*) Gonioscopy: Gonioscopy, although largely responsible for the evolution of the mechanical theory of origin of glaucoma, has contributed nothing strikingly new

31. Prijot, E., and Weekers, R.: Measurement of Resistance to the Outflow of Aqueous Humor in Chronic Glaucoma by Means of the Compression Test Using the Electronic Tonometer, Bull. Soc. belge opht. **98**:353, 1951; Tonographic Measurement of the Resistance to Aqueous Outflow in Normal Human Eyes, Ophthalmologica **123**:1, 1952.

32. Weekers, R., and Prijot, E.: Tonographic Measurement of Resistance to Aqueous Outflow in Glaucomatous Eyes, Ophthalmologica **123**:114, 1952.

33. Wortham, E.: Experimental Pupil-Block Glaucoma, Am. J. Ophth. **35**:477, 1952.

during the past year. Posner [34] emphasizes that gonioscopy is not necessary for the routine diagnosis of primary glaucoma because critical examination with a slit lamp gives almost as reliable information in determining angle depth. In general, this is true, but the method is not as infallible as gonioscopy, and little can be learned of the contour of the angle.

Posner stresses the importance of gonioscopy for evaluating pathologic changes in the angle, such as the presence of capsular material, excessive amounts of pigment, and peripheral anterior synechia. He mentions the importance of postoperative study to find the reasons for success or failure of a given operative procedure. Trantas [35] raises the question as to whether the red ring seen in the angle of the anterior chamber is the canal of Schlemm, as nearly all workers in the field assume it to be. He expresses doubt that peripheral synechia is an etiologic factor in glaucoma. Most workers now believe that synechia is the result, and not the cause, of glaucoma. Two review articles on gonioscopy, by Ogino [36] and Weinstein and Forgacs,[37] respectively, have appeared during the past year, both of which confirm gonioscopic observations previously made and summarize the practical importance of the method.

(*c*) Aqueous Veins: Several excellent papers on aqueous veins have been added to the literature during the past year. Ascher [38] reviews the literature from the time of his initial report, in 1942, until the present time and reevaluates the status of aqueous veins. His paper is most appropriate because of the increasing importance being assigned to these vessels.

In another paper, Ascher [39] suggests a more accurate terminology to be used in referring to aqueous vessels and some of the phenomena he observed within them. He would reserve the term "aqueous veins" for the "pure aqueous-containing vessels," which originate at or near the limbus from the limbal meshwork or as a scleral emissary. He suggests calling the vessel into which such veins empty the "recipient vein," rather than a "laminated vessel," and he prefers the term "aqueous-influx phenomenon" to the "positive glass-rod test phenomenon" and the "blood-influx phenomenon" to the "negative glass-rod phenomenon." He also prefers the term "collectors," or "collector trunks," to the term "outlets of Schlemm's canal."

The anatomical relationship of the aqueous veins to the canal of Schlemm was finally established a year ago by the beautiful work of Ashton, who made neoprene® (a polymer of chloroprene) casts of Schlemm's canal and the aqueous veins. By this method, he established the direct connection of the veins with Schlemm's canal. This year, he [40] supplements that work by reporting similar studies on an eye which

34. Posner, A.: Role of Gonioscopy in Glaucoma, Eye, Ear, Nose & Throat Month. **31**:210, 1952.

35. Trantas, A.: Two Controversial Gonioscopic Problems, Oto-nöre-Oftal. **5**:141, 1950.

36. Ogino, N.: Studies on the Chamber Angle by Using a Newly Devised Contact Glass and the Biomicroscope: II. Findings in Glaucomatous Eyes, Acta Soc. ophth. jap. **55**:147, 1951.

37. Weinstein, P., and Forgacs, J.: Practical Evaluation of Gonioscopic Statements, Ophthalmologica **122**:357, 1951.

38. Ascher, K. W.: Aqueous Veins: Their Status 11 Years After Their Detection, read before Section on Ophthalmology, American Medical Association, June 9-13, 1952.

39. Ascher, K. W.: Terminology of the Biomicroscopically Visible Elimination of Aqueous Humour, Docum. ophth. **5-6**:193, 1951.

40. Ashton, N.: Anatomical Study of Schlemm's Canal and Aqueous Veins by Means of Neoprene Casts: I. Aqueous Veins, Brit. J. Ophth. **36**:265, 1952.

had been enucleated because of malignant melanoma of the posterior choroid. Prior to operation a pure aqueous vein was found and its location identified by a tantalum-wire suture loosely tied around the vessel. Neoprene® was then injected into Schlemm's canal and a cast prepared. His article contains excellent illustrations made from these preparations which show that aqueous veins connect directly with the canal of Schlemm.

Thomassen and Bakken [7] carried out similar anatomical studies, the results of which were in agreement with those of Ashton. They used a somewhat different approach to accomplish the same purpose. India ink was injected into the anterior chamber of eyes which were to be enucleated for choroidal melanoma. The ink flowed promptly into the aqueous veins and served to identify them when studied in serial sections. The course of 10 such vessels was followed, and all originated in Schlemm's canal. During their course through the sclera, they seemed to have one or more connections with intrascleral blood-containing veins. Before the aqueous vein emptied into this blood vein, the two vessels for a distance ran side by side in a rigid scleral canal. During this portion of their course they shared a common canal in the rigid tissue of the sclera, separated from each other only by the wall of the vein and the layer of endothelium making up the wall of the aqueous vessel. It is in this canal that Thomassen and Duke-Elder have suggested that increased venous pressure might cause the vein to compress the aqueous vessel and impede flow of aqueous from the eye.

Studies to date more or less agree upon the phenomena observed in the aqueous veins of normal and glaucomatous eyes. Great argument arises as to their interpretation. It has been repeatedly noted in cases of chronic simple glaucoma that after pressure upon the recipient vessel a short distance beyond the point where the aqueous vein empties into a blood-filled vein blood regurgitates into the aqueous vessel. This phenomenon has been termed "the negative glass-rod phenomenon," although, as stated above, Ascher now prefers to call it "the blood-influx phenomenon." Thomassen and Bakkan [7] and Duke-Elder [8] state that the blood-influx phenomenon occurs only during periods of rising tension in the diurnal curve, whereas the "aqueous-influx phenomenon" is characteristic of the phase of decreasing pressure.

The blood-influx phenomenon might be explained in one of two ways: 1. Owing to an obstruction in the trabeculum-canal of Schlemm mechanism, aqueous flows into the aqueous veins at a reduced rate and pressure. Ascher suggests that narrowing of the outlets of the canal of Schlemm might be at fault by preventing the aqueous ready entrance to the aqueous vessels. Blood, therefore, easily regurgitates into the aqueous vessel. Goldmann [41] found the outflow of aqueous through the aqueous veins to be markedly diminished in chronic simple glaucoma and interpreted this decreased outflow as due to increased resistance to flow through the trabeculum in glaucoma. He believes, as does Ascher, that diminished flow of aqueous permitted influx of blood into the aqueous veins. 2. The venous pressure might be high, as suggested by Thomassen, and as a result displace aqueous from the aqueous veins.

41. Goldmann, H.: Pressure Rapidity of Outflow, and the Resistance to the Circulation of the Aqueous Humour in Man, Documenta ophth. **5-6**:278, 1951; Reply, Ophthalmologica **122**:191, 1951; Origin of Ocular Hypertension in Primary Glaucoma, Ann. ocul. **184**:1086, 1951.

Gaba [42] concurs with Thomassen. Phenomena which have been observed in aqueous veins, then, can be explained by either the neurovascular or the mechanical theory of glaucoma, depending upon one's point of view.

Other evidence which might be of significance has been presented by Weekers and Prijot. Greaves and Perkins,[43] on the basis of prior work by Weekers and Prijot which showed that the instillation of epinephrine into the eyes of rabbits constricted the aqueous veins and caused an associated rise in tension, stimulated the cervical sympathetic chain of the rabbit and then observed an apparent increase in drainage of aqueous into the aqueous veins of the rabbit. This could well have been due to an increased amount of aqueous being forced from the eye as a result of contraction of the smooth muscle fibers of the orbit, and hence is a passive phenomenon rather than the result of constriction of aqueous veins. Huggert [44] observed increases in intraocular pressure, at times amounting to 10 mm. Hg or more, in several eyes after the wearing of contact lenses. He interpreted this as being due to diminution in outflow of aqueous.

Two papers report the development of aqueous veins in corneal scars. Löhlein [45] believes that this was evidence that aqueous veins did not arise from Schlemm's canal but, instead, that they might represent direct connection between the anterior chamber and the cornea. Trantas [46] also observed a newly formed aqueous vein in a corneal scar, but it was his opinion that this had nothing to do with the circulation of the aqueous humor. These points of view do not seem valid in view of the work of Ashton [40] and Thomassen and Bakken,[7] although no newly formed vessels, such as have been described in this article, have ever been studied histologically.

3. *Miscellaneous Factors.*—(*a*) Heredity: The importance of heredity in ophthalmology is being increasingly realized as a result of the writings of Falls, Sorsby, Franceschetti, and others. This is particularly true in the field of glaucoma. Sorsby,[47] in his recent textbook on "Genetics in Ophthalmology," thoroughly reviews the heredity of glaucoma. He states that the familial occurrence in 20% of patients with juvenile glaucoma was not strikingly different from that found in all types of primary glaucoma. François, Deweer, and van den Berghe [48] studied a series of patients with chronic simple glaucoma and found that almost 50% had a family history of glaucoma. Biro,[49] in 1939, found heredity a factor in 5.6% of 761 patients.

42. Gaba, V.: Glaucoma and Resistance of the Sclerocorneal Trabeculum, Československ. oftal. **7**:251, 1951.

43. Greaves, D. P., and Perkins, E. S.: Influence of the Sympathetic Nervous System on the Intraocular Pressure and Vascular Circulation of the Eye, Brit. J. Ophth. **36**:258, 1952.

44. Huggert, A.: Increase of Intra-Ocular Pressure When Using Contact Lenses, Acta ophth. **29**:474, 1951.

45. Löhlein, H.: Observations on a Corneal Aqueous Vein and the Question of Its Origin, Klin. Monatsbl. Augenh. **119**:618, 1951.

46. Trantas, N.: Formation of the Laminary Veins and Ascher's Veins, Bull. Soc. hellen. ophth. **18**:57, 1950.

47. Sorsby, A.: Genetics in Ophthalmology, London, Butterworth & Co., Ltd., 1951.

48. François, J.; Deweer, J. P., and van den Berghe, J.: Chronic Simple Glaucoma with Dominant Heredity, Ann. ocul. **184**:404, 1951.

49. Biro, I.: Notes upon the Question of Hereditary Glaucoma, Ophthalmologica **122**:228, 1951.

In 1951 he studied 125 patients and found a hereditary incidence of 12.8%. He believes that both figures are too low. Goldschmidt [50] reaches the conclusion that the inheritance of glaucoma was either sex-linked or due to a recessive factor. Other associated or contributing causes for glaucoma are suggested.

(*b*) Retinitis Pigmentosa: Panepinto and Locascio [51] studied 42 patients with retinitis pigmentosa and found evidence of glaucoma in only one patient. They believe that this result refutes any probable relationship of the two diseases.

(*c*) Systemic Diseases: Courtis and Nunez,[52] in a clinical study of 120 patients with glaucoma, found the following associated diseases: vascular disease, in 44%; allergic diseases, in 14%; rheumatism, in 40%, and hepatic disorders, in 43%. Other secondary factors, such as the menopause, emotional disturbances, and the influence of the menstrual cycle, are discussed.

B. Diagnosis

1. *General Considerations.*—There is great need for improvement in our methods of diagnosis of glaucoma. Although our understanding of the disease and methods of treatment are improving, successful therapeutic results continue to depend upon early diagnosis. This can be made only by suspecting the presence of the disease in every patient regardless of age and by carrying out a complete ophthalmologic examination, with determination of visual fields, tonometry, and provocative tests as indicated.

Brav and Kirber [53] conducted mass screening tests for glaucoma on supposedly normal persons which consisted of recording visual acuity, making external and ophthalmoscopic examinations, and measuring the ocular tension. They found that 1.53% of the persons examined had definite glaucoma, whereas 0.71% of the age group of 40 to 65 years had a borderline condition. Their results offer sufficient evidence that all patients over the age of 40 should have routine ocular examinations with recording of tension. This is of great importance because the diagnosis should be made before the stage of cupping of the optic nerve and the development of visual-field defects. In addition, careful note should be made of angle depth by examination with a slit lamp or gonioscope, careful provocative tests, and repeated ocular-tension measurements whenever the anterior chamber is shallow and the angle narrow, even though the tension is well within normal limits. If this routine study is not done, the diagnosis of narrow-angle glaucoma will be missed during the interval between attacks and in the preglaucoma stage because the ocular tension is characteristically normal.

Pichette and Audet [54] emphasize the fact that glaucoma is a universal disease and discuss its gravity in Canada, where it accounts for approximately 15% of the

50. Goldschmidt, R. B.: A Not Dominant Glaucoma Pedigree, J. Hered. **42**:271, 1951.

51. Panepinto, B., and Locascio, G., Jr.: Association of Retinal Pigmentary Degeneration with Glaucoma, Gior. ital. oftal. **4**:209, 1951.

52. Courtis, B., and Nunez, R. B.: General Clinical Study on Glaucoma, Día méd. **23**:3360, 1951.

53. Brav, S. S., and Kirber, H. P.: Mass Screening for Glaucoma, J. A. M. A. **147**:1127, 1951.

54. Pichette, H., and Audet, J.: Prevention in the Fight Against Glaucoma, Laval méd. **16**:597, 1951.

total number of the blind. Pavia [55] discusses participation of the general practitioner in glaucoma surveys by the measurement of ocular tension. The objection to such a method of survey is the false sense of security which the patient might gain. The general practitioner, obviously, would detect the disease only in those patients who show definite elevation of ocular tension. Borderline, chronic simple (wide-angle) glaucoma, and narrow-angle glaucoma during the interval between attacks would be missed. Howland [56] publishes an excellent article directed toward orientation of the general practitioner. One of the important phases of any glaucoma program is the alerting of practitioners in all branches of medicine to signs suggestive of the disease. Howland states that 24% of blindness in the state of Delaware is caused by glaucoma. Pichette and Audet [57] discuss the advantages of glaucoma clinics, the number of which is being constantly increased. Such clinics are of particular value in the study of difficult problems which require highly specialized care and for the training of residents in the management of the glaucoma. Alvaro and de Toledo [58] point out the effectiveness of glaucoma clinics in obtaining excellent follow-up care.

2. Tonometry.—Accurate and standardized tonometers are essential to the successful management of glaucoma. The problem has been solved in a very practical way in this country by the Committee for Standardization of Tonometers of the American Academy of Ophthalmology and Otolaryngology. New instruments continue to be introduced, but usually on a laboratory basis. One new instrument has been introduced by Maurice,[59] which he calls an aplanation tonometer. It is based on the principle that a plane surface would be established between the cornea and an inflated membrane pressed against it when the pressure inside the membrane is equal to the intraocular pressure. He claims that his instrument gives absolute readings to within an accuracy of 1 mm. Hg and has a sensitivity of about 2% of the intraocular pressure. The disadvantage is such a fast reaction time that changes in intraocular pressure due to the pulse and respiration are recorded. From the description, this instrument might prove to be an excellent research tool, and possibly practical for routine use.

New developments in tonometric studies are yielding information of diagnostic importance. Grant's [2] method of tonography may have its greatest value as a diagnostic test, particularly in patients with borderline chronic simple (wide-angle) glaucoma. If his findings are correct, a diminished aqueous outflow would indicate the presence of glaucoma. This is emphasized in an excellent article by Posner,[60] and a practical way of applying it is described.[61]

55. Pavia, J. L.: Collaboration of the General Practitioner in the Prevention of Blindness from Glaucoma in the United States, Rev. oto-neuro-oftal. **25**:131, 1950.

56. Howland, A. W.: Glaucoma—Its Present Concept, Delaware M. J. **23**:180, 1951.

57. Pichette, H., and Audet, J.: Prevention in the Control of Glaucoma, Canad. M. A. J. **66**:1, 1952.

58. Alvaro, M. E., and de Toledo, R.: Glaucoma Clinics in Brazil, Sight-Saving Rev. **21**:161, 1951.

59. Maurice, D. M.: An Aplanation Tonometer of New Principle, Brit. J. Ophth. **35**:178, 1951.

60. Posner, A.: Tonography as a Routine Procedure, Eye, Ear, Nose & Throat Month. **31**:260, 1952.

61. Posner, A.: Tonography as a Routine Procedure, Eye, Ear, Nose & Throat Month. **31**:321, 1952.

Kleinert,[62] in an excellent follow-up article to a paper previously published in collaboration with Grun, suggests that a phenomenon observed in aqueous veins, called the compensation maximum, be utilized as a diagnostic test. Kleinert and Grun had noted that blood may regurgitate backward from the episcleral veins into aqueous veins when a critical level of pressure, termed the compensation maximum, is applied to the eye. In cases of chronic simple (wide-angle) glaucoma this occurs when 100 gm. Hg or less is applied to the globe, whereas in normal eyes reversal does not occur until the pressure is 150 gm. or over, and then only in 8% of eyes. It is interesting that eyes with narrow-angle glaucoma respond to this test during the interval between attacks in the same way as do normal eyes. During acute attacks the test was not possible because aqueous veins then are invisible. In suspected cases of glaucoma, Kleinert's test appeared reliable and of practical value.

Duke-Elder [3] and Langley and Swanljung [4] believe that variations in ocular tension of more than 5 mm. are suggestive of glaucoma. Duke-Elder [3] discusses what he terms the "bulbar-pressure" test. A pressure of 25 gm. is exerted upon the eye for two minutes. In the normal eye the tension is low upon removal of the weight but rapidly rises to the normal level, which is never exceeded. If this is done to a glaucomatous eye during the period of rising tension, the application of 25 gm. of weight causes little or no lowering of tension in the glaucomatous eye, as compared with the normal eye, and is accompanied by a significant reactive rise in pressure, which may be of diagnostic value. He states that the glaucomatous eye behaves like a normal eye during periods of decreasing tension. He terms this the bulbar-pressure test.

3. *Perimetry.*—There has been no change in the status of perimetry. It remains a reliable diagnostic test and our most dependable method of evaluating therapy. Van Wien [63] investigated the significance of visual fields taken with minute light stimuli in dark-adapted eyes in cases of early glaucoma but found that the method offered no advantages in the early diagnosis of glaucoma. In patients with early glaucoma Ferraris de Gaspare [64] observed that during provocative tests, even if negative, visual-field studies often demonstrated an enlarged blind spot which previously could not be elicited. This did not occur in subjects with normal eyes. Kadlecova [65] makes a detailed review of the origin of glaucomatous visual-field defects. He believes that glaucomatous scotomata result from nerve-fiber damage rather than, as Evans thought, on a vascular basis.

4. *Provocative Tests.*—The search is being continued for more accurate and reliable provocative tests. Promising tests are being developed which utilize tonometric studies. The reader is referred to Grant's method of tonography,[2] studies of diurnal variation in tension,[66] bulbar-pressure tests,[3] and the compensation-maximum test,[62] which have been described elsewhere.

62. Kleinert, H. W.: The Compensation Maximum: A New Glaucoma Sign in Aqueous Veins, A. M. A. Arch. Ophth. **46**:618, 1951.

63. Van Wien, S.: Significance of Visual Fields Taken with Minute Light Stimuli in Dark-Adapted Eyes in Early Glaucoma, Am. J. Ophth. **35**:951, 1952.

64. Ferraris de Gaspare, P. F.: Additional Diagnostic Data on Scotometry in Chronic Glaucoma, Boll. ocul., p. 677, November, 1951.

65. Kadlecova, V.: Genesis of Glaucomatous Scotomata, Československ. oftal. **7**:8, 1951.

66. Duke-Elder,[3] Langley and Swanljung.[4]

Ferraris de Gaspare,[64] somewhat along the lines of Bietti's work of a year ago, suggests a provocative test consisting of visual-field studies done while the water-provocative or the caffeine test was being carried out.

Posner [67] reviewed the various diagnostic tests for glaucoma. He depends upon the lability test of Bloomfield and Lambert, the water-provocative test of Schmidt, and the dark-room test. Imai and Shimizu [68] conducted studies on the value of the Bloomfield test and concluded that it was valuable for the early diagnosis of chronic simple glaucoma. Kaminskaya, Kaplan, and Belousova [69] suggest a provocative test which is done by injecting isotonic saline solution into the skin of the arm. The site of the swelling disappears more quickly in glaucomatous patients than in normal persons. When this was done on the temple, absorption was even more rapid than on the arm. Ross [70] made a careful study of 200 unselected white male subjects in evaluating the lability test from a gonioscopic point of view. Of the 200 patients, 196 showed negative results. One patient showed a rise to 30 mm. Hg and three patients to more than 30 mm. One must conclude that the test, as he did it, gave very few false-positive responses.

C. Medical Treatment of Glaucoma

1. *Miotics.*—(*a*) Diisopropyl Fluorophosphate: Bayo and de la Pena [71] and Moreu Gonzales-Pola [72] each describe experiences with diisopropyl fluorophosphate and attest to its efficacy. Thomas, Cardier, and Algan [73] state that it gave its most constant results in aphakic glaucoma, a statement with which nearly all workers agree. In other types of glaucoma, they believe that the drug was useful usually only to lower tension prior to operation. Swan and Gehrsitz,[74] in a careful paper, confirm Leopold's observation that the instillation of physostigmine prior to use of diisopropyl fluorophosphate diminished the effectiveness of the latter. They found, also, that pilocarpine somewhat reduced the reactivity of the iris sphincter to both physostigmine and diisopropyl fluorophosphate. Swan's observations are of particular importance in cases of acute glaucoma, in which it has been the practice of many ophthalmologists to use combinations of pilocarpine and physostigmine to

67. Posner, A.: Remarks on the Diagnosis of Early Glaucoma, Eye, Ear, Nose & Throat Month. **30**:152, 1951.

68. Imai, S., and Shimizu, E.: Study on the Lability Test of Bloomfield and Lambert, Acta Soc. ophth. jap. **55**:160, 1951.

69. Kaminskaya, Z. A.; Kaplan, A. I., and Belousova, L. B.: The Hydrophile Test of McClure, Vestnik oftal. **30**:18, 1951.

70. Ross, M. G.: Lability Test and Gonioscopy in Diagnosis of Glaucoma, Am. J. Ophth. **35**:25, 1952.

71. Bayo, J. M., and de la Pena, A.: Synthetic Parasympathomimetics with an Indirect Peripheral Action: Preliminary Experimental Study on the Miosis, Intraocular Pressure, and Uveal Permeability Produced by Diisopropyl Fluorophosphate, Diethyl *p*-Nitrophenylphosphate and Diisopropyl *p*-Nitrophenylphosphate, Arch. Soc. oftal. hispano-am. **10**:1310, 1950.

72. Moreu Gonzales-Pola, A.: New Pharmacological Treatment of Glaucoma Verum: First Trials with Diisopropyl Fluorophosphate, Dihydroergotamine (DHE45), and "Ethycol," Arch. Soc. oftal. hispano-am. **11**:50, 1951.

73. Thomas, C.; Cardier, J., and Algan, B.: Utilization of Diisopropyl Fluorophosphate in Certain Forms of Ocular Hypertension, Bull. Soc. opht. France **8**:847, 1951.

74. Swan, K. C., and Gehrsitz, L.: Competitive Action of Miotics on the Iris Sphincter, A. M. A. Arch. Ophth. **46**:477, 1951.

obtain a synergistic effect. The action of pilocarpine and diisopropyl fluorophosphate together is stronger than that of pilocarpine alone, but weaker than when either diisopropyl fluorophosphate or physostigmine is used alone. This might be an argument for using diisopropyl fluorophosphate in the treatment of acute glaucoma, but several reports are now available in the literature of acute attacks of glaucoma following the use of diisopropyl fluorophosphate. One was that of a patient observed by Butler [75] during the past year.

(*b*) Furtrethonium Iodide (Furmethide®): Only one paper was published during the past year reporting the use of furtrethonium iodide. This paucity undoubtedly was due to removal of the drug from the market because of its irritative effects. It was found to cause thickening of the conjunctiva, and not infrequently dacryostenosis, as described by Shaffer and Ridgway.[76] Withdrawal of furtrethonium iodide was a real loss, because its physiological and clinical properties made it an extremely valuable miotic agent. Goodwin,[77] in 1951, conducted further studies on the properties of furtrethonium iodide. He found that its use following local instillation into normal eyes reduced the tension 5.1 mm. Hg in one hour. The decrease was more marked in primary glaucoma and was greater in chronic simple glaucoma than in narrow-angle glaucoma. The drug was also more effective in narrow-angle glaucoma when no congestion was present. In all eyes the reduction in tension was less if visual-field defects were pronounced.

(*c*) Pilocarpine: De Grosz and Kedvessy [78] review the pharmacology of pilocarpine, particularly pilocarpine hydrochloride. They state that pilocarpine slowly loses its effectiveness in aqueous solution, but does remain effective for at least 30 days. Eidelman [79] found the comparative strengths of carbachol, prostigmine, and pilocarpine to be approximately the same, but physostigmine somewhat more effective. Magitot [80] discusses in a general way the status of the medical treatment of glaucoma and divides its development into three stages: (1) from 1876 to 1934, a period characterized by use of pilocarpine and physostigmine; (2) from 1934 to 1940, in which such synthetic drugs as carbachol (doryl®) and methacholine (mecholyl®) were developed; (3) from 1940 to the present time, a period during which such synthetic drugs as diisopropyl fluorophosphate, furtrethonium iodide, and dibenamine® (N-n-dibenzyl-β-chloroethylamine) were introduced.

2. *Sympatholytic Drugs.*—(*a*) Dibenamine®: Mullen and Leopold [81] investigated the usefulness of adrenergic blocking agents in both primary and secondary

75. Butler, W. E.: Acute Glaucoma Reported by DFP, Am. J. Ophth. **35**:1031, 1952.

76. Shaffer, R. N., and Ridgway, W. L.: Furmethide Iodine in Production of Dacryostenosis, Am. J. Ophth. **34**:718, 1951.

77. Goodwin, R. C.: Changes in Intraocular Pressure in Normal and Glaucomatous Eyes Following Furmethide, Am. J. Ophth. **34**:1139, 1951.

78. de Grosz, E., and Kedvessy, G.: Standardization of Pilocarpine Solutions, Arch. opht. **11**:155, 1951.

79. Eidelman, B. M.: Comparative Action of Carbachol, Pilocarpine, Physostigmine, and Prostigmine on the Intraocular Tension, Vestnik oftal. **30**:34, 1951.

80. Magitot, A.: What Should One Think of the New Drugs Used in Glaucomatous Hypertension? Ann. ocul. **184**:1106, 1951.

81. Mullen, C. R., and Leopold, I. H.: Adrenergic Blocking Agents in Treatment of Glaucoma, A. M. A. Arch. Ophth. **46**:549, 1951.

glaucoma. All other types of therapy were discontinued for 6 to 12 hours before using these substances. Dibenamine,® piperoxan (benodaine®) and dihydroergocornine were given systemically. The authors found that dibenamine® was the most effective and at times lowered intraocular pressure in some glaucomatous eyes when other means of therapy were ineffective. Piperoxan was the least effective of the three agents which they employed. They concluded, however, that the effect of adrenergic blocking agents was unpredictable. Moreu Gonzales-Pola [82] reported the results obtained with dihydroergotamine (DHE45) and stated that it is only an accessory form of medication. Bernsmeier and Pau [83] describe the use of Compound Ciba 9295 (n,n,n′,n′,3-pentamethyl-n,n′-diethyl-3-azapentane-1,5-diammonium-dibromide), a new adrenergic blocking agent. They found that it lowered the ocular tension but that the effect lasted only one to two hours in normal eyes.

(*b*) Hormonal Therapy: Radnót [84] reports a case in which an attack of glaucoma developed after administration of testosterone. He believes, therefore, that this type of therapy is contraindicated for other conditions in the presence of glaucoma. Treumer [85] treated several patients by the intramuscular and intravenous injection of corpus-luteum hormone, with no beneficial effect. He believes this observation refutes Obal's report.

D. Surgical Treatment

Although views as to the mechanism of origin of glaucoma continue to differ, agreement is more or less general upon the indications for surgery and the choice of operation. It is well known that eyes with chronic glaucoma respond unpredictably to surgery and as a result of operation are left badly mutilated. It is generally believed, therefore, that medical treatment is indicated as long as the disease can be kept under control, as determined by repeated careful recording of ocular tension and visual fields. The operation of choice for this type of glaucoma is usually one of the filtering procedures, such as corneoscleral trephination or iridencleisis or some modification of either. Cyclodiathermy is increasing in popularity, and cyclodialysis has its loyal supporters.

Acute glaucoma, on the other hand, responds well to rather simple surgical procedures if performed early. Without surgical intervention these eyes are subject to acute congestive attacks at any time, in spite of a miotic regimen. Prompt surgical treatment is indicated, either during the attack, if it continues unabated with use of miotics, or during the interval between attacks.

Even proponents of the neurovascular school of origin of glaucoma concede the value of preoperation and postoperative gonioscopic examinations of glaucomatous eyes. Gonioscopy gives a familiarity with the anatomy of the angle of the anterior chamber of the living eye which is difficult to obtain in any other way.

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82. Moreu Gonzales-Pola, A.: New Methods of Pharmacotherapy in True Glaucoma, Arch. Soc. oftal. hispano-am. **11**:50, 1951.

83. Bernsmeier, A., and Pau, H.: Ganglionic Block Produced by 9295 (Ciba): Its Effect upon Blood Pressure and Normal and Increased Ocular Tension, Arzntl.-Forsch. **2**:69, 1951.

84. Radnót, M.: Effect of Hormones in Cases of Glaucoma, Szemészet ophth. hungary **88**:114, 1951.

85. Treumer, K.: Treatment of Glaucoma with Corpus-Luteum Hormone, Klin. Monatsbl. Augenh. **118**:644, 1951.

Such an eminent leader of the neurovascular school as Sir Stewart Duke-Elder [86] emphasizes the importance of preoperative knowledge of the angle, best obtained by gonioscopic study. For example, he states that the choice between a corneoscleral trephination and an iridencleisis is often made after gonioscopic evaluation of the depth and contour of the angle of the anterior chamber. A corneoscleral trephination should not be done if the angle is very narrow because of danger of injuring the lens or incarceration of lens, iris, or ciliary process into the opening, thereby precluding success of the surgical procedure.

Much can be learned through gonioscopic study of the reasons for success or failure of a given operation. We have learned that corneoscleral trephination usually fails, as a result of scarring or binding down of Tenon's capsule and the conjunctiva over the region of the trephine opening. Less often, obstruction of the inner aspect of the opening may occur by incarceration of intraocular structures. Information as to the mechanism of action of certain operations may be gained. For example, the finding of a cleft after cyclodialysis suggests suprachoroidal drainage and absorption of aqueous as the means by which that operation controls ocular tension. Such an observation supports histological studies by Elschnig and Barkan.

Several excellent review articles on the surgical treatment of glaucoma have appeared during the year. Moreu Gonzales-Pola [87] discusses the indications for surgery. He advocates cyclodialysis for chronic simple glaucoma when the angle is open. Atkinson,[88] in an excellent paper, reviews the indications for iridectomy, cyclodialysis, and filtering procedures, describing his technique in detail. Van Beuningen [89] discusses some of the difficulties encountered in doing filtering operations. He, also, presents his indications for various types of procedures in eyes of various angle widths. He stresses the importance of careful preoperative gonioscopic examination of the angles. Venable [90] reports his observations on the management of glaucoma in the Negro. His paper is supplemented by an excellent discussion presented by a group of distinguished ophthalmologists. The consensus is that the problem of glaucoma in the Negro is little different from that in persons of the white race except for a tendency to postoperative scarring following filtering procedures.

1. *Iridectomy.*—Chandler,[30] in a comprehensive article on narrow-angle glaucoma, voices full support of the mechanical origin of the disease and advises peripheral iridectomy early in its course. In the later stages, when the angle is rather extensively closed by peripheral anterior synechia, he suggests a modified iridectomy which he has devised. He introduces a cyclodialysis spatula through a limbal incision at 12 o'clock to free gently the synechia around the upper half of the globe. Iridectomy is then done in the regular way. Careful wound closure is obtained by

86. Duke-Elder, S.: The Problem of Glaucoma, Los Angeles, Calif., Jan. 1952.

87. Moreu Gonzales-Pola, A.: At What Time and by Which Method Should Operation for Glaucoma Be Done? Arch. Soc. oftal. hispano-am. **11**:40, 1951.

88. Atkinson, D. T.: Surgical Approach to Glaucoma, J. Internat. Coll. Surgeons **16**:58, 1951.

89. van Beuningen, E. G. A.: A Few Problems of Filtering Operations Observed with the Gonioscope, von Graefes Arch. Ophth. **151**:541, 1951.

90. Venable, H. P.: Glaucoma in the Negro, J. Nat. M. A. **44**:7; 196, 1952.

Verhoeff tract sutures. Haas and Scheie [5] also report good results from peripheral iridectomy and advocate its use early in the course of the disease. Beckett,[91] Posner,[92] and Goldberg [93] also advocate iridectomy for acute glaucoma.

Riesenhampff [94] describes a technique for performing iridectomy in ambulatory patients. He introduces a Graefe knife at the limbus as for cataract extraction and extends the incision upward, but does not complete it. A bridge of scleral tissue is therefore left superiorly. The iris forceps is introduced into the wound on either side and the iris segment incised. The incision made with the Graefe knife is varied according to the width of the coloboma desired.

2. *Iridencleisis.*—A review of the literature during the past three years indicates that the use of iridencleisis is increasing. This procedure is particularly indicated, according to most authors, (1) for advanced narrow-angle glaucoma in eyes in which the tension is persistently elevated, probably owing to the formation of extensive anterior peripheral synechia, and (2) for chronic simple glaucoma in which the angles are sufficiently narrowed or crowded to render corneoscleral trephination dangerous to the lens and subject to failure from incarceration of intraocular structures.

Dunnington [95] states that iridencleisis is better done through a perpendicular scleral incision than through a shelving incision. The edges of a shelving incision act like a valve and tend to close more rapidly and firmly than those of the perpendicular type. He advises surgery in cases of chronic simple glaucoma only when evidence of deterioration of the eye occurs in spite of medical therapy.

Meyer [96] reviews the results in 207 iridencleises which he performed. He believes that iridencleisis primarily lowers the tension through its effect upon the neurovascular mechanism, and he cites the normalization of tension in the presence of a flat scar to support his reasoning. He believes that in eyes with a cystic scar there is probably an added filtering effect superimposed upon the neurovascular mechanism. He thinks that a cystic scar at times might modify the corneal elasticity and that the tonometric readings might be altered by the cystic cavity, which could constitute a decompression chamber. In his series of patients the tension was normalized without miotics in 87% of eyes with acute narrow-angle glaucoma and in 65% of eyes with secondary glaucoma. He used an ab externo incision and incarcerated the iris with or without an iridotomy.

Hébert [97] reports 150 iridencleises performed since 1937. He also used an ab externo incision and employed a special knife devised by Weekers in 1934, in which the knife blade is bent almost at right angles to the handle. This instrument is said to facilitate cutting of the conjunctival flap and making of the scleral incision.

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91. Beckett, H. C.: Primary Glaucoma, M. J. Australia **2**:113, 1951.
92. Posner, A.: Physiologic Basis of Glaucoma, Eye, Ear, Nose & Throat Month. **30**:432, 1951.
93. Goldberg, H. K.: Results of Various Operative Procedures in Acute Congestive Glaucoma, Am. J. Ophth. **34**:1376, 1951.
94. Riesenhampff, J.: Bilateral Knife Iridectomy, Klin. Monatsbl. Augenh. **118**:641, 1951.
95. Dunnington, J. H.: Surgical Treatment of Primary Glaucoma, Am. J. Ophth. **34**:1756, 1951.
96. Meyer, S. J.: Physiopathology and Technique of Iridencleisis, Am. J. Ophth. **35**:788, 1952.
97. Hébert, E.: Iridencleisis and Its Instrumentation, Arch. opht. **11**:172, 1951.

3. *Corneoscleral Trephination.*—Corneoscleral trephination and iridencleisis continue to be the two most widely done operations for chronic simple glaucoma. The technique has become fairly well standardized. Dunnington [95] emphasizes an important technical point when he insists upon accurate closure of Tenon's capsule to preserve the sub-Tenon-capsule space and to prevent retraction of Tenon's capsule downward into the area of the trephine opening, which might lead to closure.

Arkin [98] describes a modification of corneoscleral trephination in which he introduces a spatula between the sclera and the ciliary body to protect the uveal tract from injury during the preparation of the trephine button.

Kronfeld [99] reports studies which he believes demonstrated the transconjunctival passage of aqueous through the conjunctiva after filtering operations. He concludes that aqueous escapes through the conjunctiva as well as by subconjunctival filtration and absorption. He analyzed for ascorbic acid samples of aqueous blotted up on filter paper which had been placed over the filtering site. These specimens contained much more of the acid than lacrimal fluid from the same eye. He reasoned that the high ascorbic-acid content identified the fluid on the filter paper as aqueous which had left the eye through the conjunctiva overlying the filtering cicatrix.

4. *Sclerectomy and Sclerotomy.*—Sclerectomy and sclerotomy are being employed only occasionally as judged from the literature. Sclerectomy is probably most frequently combined with iridencleisis in eyes with rather high levels of ocular tension.

Foroni [100] describes a technique for sclerotomy in which a 7-mm. incision is made parallel to the limbus, followed by the placement of an incision extending vertically about 3 mm. from the middle of the first incision, to form two small triangular flaps, which act like a valve. The conjunctival flap is prepared beforehand, as in corneoscleral trephination. The author was not able to evaluate the results in a significant number of patients.

Goldberg [93] reports results from posterior sclerotomy alone or in combination with other operations in 32 eyes. Failure resulted in 29 eyes, owing to surgical complications, such as vitreous hemorrhage, retinal detachment, cataract, or recurrence of elevated tension with subsequent loss of vision. The operations, however, were done in cases of far-advanced glaucoma. Goldberg concludes that iridencleisis is the operation of choice.

5. *Cyclodiathermy.*—Cyclodiathermy is enjoying a second wave of enthusiasm, largely as a result of the work of Weekers, in Europe, and Castroviejo, in this country. Cyclodiathermy was first introduced by Vogt. His original technique involved placing as many as 100 punctures over a band extending one-third to one-half the circumference of the globe, beginning as near as 2.5 mm. behind the limbus and extending back as far as the insertion of the rectus muscles, in front of the ora serrata. The operation fell into disfavor because of its unpredictable effect upon ocular tension and the high incidence of corneal opacity, probably due to damage to the cornea by the diathermy current.

98. Arkin, W.: Modification of Elliot's Operation and Its Application to High Trephining, Klin. oczna **20**:50, 1950.

99. Kronfeld, P. C.: Chemical Demonstration of Trans-Conjunctival Passage After Antiglaucomatous Operations, Am. J. Ophth. **35**:38 (May, Pt. 2) 1952.

100. Foroni, C.: Triangular Valve Sclerotomy ab Externo, Ann. ottal. e clin. ocul. **77**:277, 1951.

Weekers uses a nonperforating electrode applied no closer than 6 to 8 mm. from the limbus and held in place for as long as 10 to 15 seconds. He makes as many as 10 to 20 applications. This method apparently has a more reliable effect in reducing ocular tension and is less prone to cause serious ocular damage than other methods. Reiser advocated a similar technique, but used a 1-mm. penetrating electrode.

Papers by the following authors, reporting results of the use of cyclodiathermy with Weeker's technique or with various modifications of his procedure, have appeared during the past year; Victoria, Gordillo, and Filgueira [101]; Votockova [102]; Cavka [103]; Knobloch [104]; Periera [105]; Scheie,[106] and Viger.[107] Victoria, Gordillo, and Filgueira [101] employed a 0.5-mm. electrode applied for about five seconds 8 to 9 mm. from the limbus. Twelve applications were made. They had good results in chronic simple glaucoma but found that the method was of little value in the congestive type. The operation was of some value in infantile glaucoma. They believe that, because of the simplicity of the operation, its harmlessness, and the fact that it could be repeated without risk, it should be a regular part of our surgical armamentarium. Cavka [103] uses the nonperforating technique combined with cyclodialysis. The pressure was controlled in 41 of 53 eyes. Knobloch [104] performs angiodiathermy, which consists of electrocoagulation in front of and parallel with the insertion of the internal and external rectus muscles. All patients operated upon for chronic simple glaucoma were permanently cured.

Scheie [106] reports the results obtained from cyclodiathermy in two series of eyes. Most of the eyes had advanced chronic simple, aphakic, or hemorrhagic glaucoma. Nearly all of them had had other operative procedures, which had failed; had only residual fields with high tension, so that filtering operations were feared, or were considered to be unsuitable for any other type of surgery. In one group, of 16 eyes, the Vogt technique was used. The tension was controlled in only seven of them. In six of the eyes there developed pronounced corneal edema and opacity, thought to be due to damage to the cornea from the cautery. This operation was discontinued in 1949 because of these discouraging results. Results obtained in a second group, of 13 eyes, operated on by a newer technique, somewhat after that of Reiser and Castroviejo, are reported. No operative or postoperative complications occurred in the 13 eyes operated on by this method. Two of the patients had been followed for less than a month, so that they were not included in the final evaluation. In the other patients, who had been followed for periods of over 1 month and for as long as 10 months, the tension had been controlled in all, two operations being required

101. Victoria, V.; Gordillo, C. H., and Filgueira, E.: Ciliary Diathermy in the Treatment of Glaucoma, Arch. oftal. Buenos Aires **26**:226, 1951.

102. Votockova, J.: Retrociliary Diathermy in Glaucoma, Českoslov. oftal **7**:239, 1951.

103. Cavka, V.: Non-Perforating Cyclodiathermy with Cyclodialysis Circumscripta in Glaucoma, Brit. J. Ophth. **35**:307, 1951.

104. Knobloch, R.: A Note on Angiodiathermy in Glaucoma, Českoslov. oftal. **7**:73, 1951.

105. Periera, R. F.: Diathermy in the Surgical Treatment of Glaucoma, Arch. oftal. Buenos Aires **26**:423, 1951.

106. Scheie, H. G.: Cyclodiathermy in the Treatment of Glaucoma, West. J. Surg. **60**:322, 1952.

107. Viger, R. J.: Cyclodiathermy Puncture Operation in the Treatment of Glaucoma, Tr. Canad. Ophth. Soc. p. 119, June 21-23, 1951.

for two eyes. No corneal damage occurred. He concludes that this newer method of cyclodiathermy seems to have more reliable effect upon tension, and is less harmful to the eye, than the old Vogt technique. He believes that the operation will have to be evaluated for a much greater length of time for definite conclusions to be drawn. Such late complications as phthisis bulbi, retinal detachment, and late rise in tension are to be watched for.

Viger [107] used essentially the old Vogt technique in 10 eyes in which other types of surgery had failed. The tension was controlled in four eyes. He concluded that the operation was of value in buphthalmos, absolute glaucoma when the patient refuses enucleation, and secondary glaucoma when other surgical methods have failed.

6. *Cyclodialysis.*—The cyclodialysis technique recently described by O'Brien and Allen is probably more widely used than any other in this country. Allen [108] has modified this technique considerably during the past year. He turns a conjunctival flap and then makes a radical incision about 3 mm. long, extending into clear cornea. The spatula is introduced to free the scleral spur on each side for a total of about 90 degrees. He lists the following advantages: (*a*) The scleral spur is divided by the incision, and the tip of the spatula is in view at all times. (*b*) There is less danger of injury to the long ciliary vessels and nerves, which penetrate the ciliary body about 3 mm. from the limbus. (*c*) An iridotomy or iridectomy can be performed with great ease if need be. He believes that if this technique is observed the operation can be of benefit in any type of glaucoma. It does not interfere with the performance of subsequent filtering operations or mar the appearance of the eye. He is of the opinion that the operation may well be indicated as an initial procedure. Roveda [109] performs cyclodialysis inferiorly in aphakic patients to avoid the area of incision. Excellent results are claimed.

The mode of action of cyclodialysis is discussed by Goldmann.[110] He agrees with Elschnig and Barkan that cyclodialysis provides for flow of aqueous into the suprachoroidal space, where it is absorbed. Goldmann noted that the pressure in the episcleral veins was 2 to 3 mm. higher than the ocular tension and that therefore no outflow pressure existed. He was unable to find aqueous veins after operation.

CONGENITAL GLAUCOMA

Congenital glaucoma may be divided into infantile and juvenile types. Infantile glaucoma occurs in children up to 2 or 3 years of age, a time when the eyeball undergoes enlargement under increased ocular tension. This stretching accounts for all the classic signs of the disease, among which are ruptures in Descemet's membrane and imbibition of aqueous by the cornea with corneal haze, usually accompanied by severe photophobia and enlargement of the eyeball, or buphthalmos. Juvenile glaucoma occurs in older children and young adults up to the age of 30 or 35 and runs the course of chronic simple glaucoma. Because it occurs at such an early age, it probably occurs at least partially on a congenital basis.

1. *Juvenile Glaucoma.*—Juvenile glaucoma may well be a transition disease between the infantile type and chronic simple glaucoma. Primary juvenile glaucoma

108. Allen, J. H.: Cyclodialysis: A Simplified Technique, South. M. J. **44**:931, 1951.
109. Roveda, J. M.: Inferior Cyclodialysis, Día méd. **23**:2282, 1951.
110. Goldmann, H.: Mode of Action of the Cyclodialysis, Ophthalmologica **121**:94, 1951.

occurs at such an early age that a congenital predisposition or a congenital anomaly seems to be a likely cause. No basis exists upon which to differentiate juvenile glaucoma and chronic simple glaucoma of adults except the arbitrarily set age limit of 30 to 35 years.

A congenital origin is supported also by the fact that the disease is often familial in nature (see section on "Heredity," page 765) and by its frequent association with other congenital anomalies. François [111] reports occurrence of juvenile glaucoma in the right eye of a 13-year-old girl associated with naevus flammeus of the right side of the face. He attributes the increased pressure to angiomatosis of the choroid. The tension was controlled by iridencleisis. Djacos and Joannides [112] report three cases of the more complete syndrome, Sturge-Weber-Krabbe disease. One patient did not have glaucoma. In addition to the lesions of the face, the patients had manifestations of involvement of the orbit and brain. Djacos and Joannides suggest that the lesion is probably based on a predisposition to impaired venous permeability, with resulting dilatation and metaplasia. They believe that the increase in ocular tension probably results from the increased production of aqueous.

The only new means of therapy revealed during the past year was that proposed by Lebensohn,[113] who suggests the use of minus lenses as an adjuvant to miotic therapy in the control of tension in juvenile glaucoma. He reports a case in which miotics had failed to control the ocular tension, but in which with the addition of a —2 sphere to the full correction the tension has remained normal for 26 months. Lebensohn theorizes that the correction was effective by causing contraction of the ciliary muscle, which, in turn, brought about a favorable vascular readjustment.

2. *Infantile Glaucoma.*—Infantile glaucoma continues to create much interest because of the progress which is being made in its treatment. At least two excellent monographs have appeared on congenital glaucoma. Kluyskens [114] reviews the entire subject and presents a survey of 214 cases which he collected, including 31 of his own. He believes that persistent embryonic tissue or other abnormalities in the angle are not sufficient to explain the elevation in tension.

The earliest possible surgical intervention is advocated. Of the cases he reviewed, goniotomy was performed in seven eyes, with control of the tension in four of the seven. He found that, although the tension may be controlled in 60% of patients, vision is preserved in only 23% regardless of the operative procedure. The great majority of the eyes in his series were treated by Elliot's corneoscleral trephination or iridencleisis. The results are much poorer than those in this country from the use of goniotomy or goniopuncture or a combination of the two.

Algan [115] presents an exhaustive review of the treatment of infantile glaucoma, in which he concludes that medical treatment is of little value. He thinks well of cyclodiathermy, done by the original Vogt technique, and reports success in 23 of 26 eyes. None, however, was observed for more than one year. He subdivides infantile glaucoma into four stages. In the first stage, in which the eye shows little

111. François, J.: Oculo-Cutaneous Angiomatosis (Lawford), Ophthalmologica **122**:215, 1951.

112. Djacos, C., and Joannides, T.: Sturge-Weber-Krabbe Disease, Ann. ocul. **184**:994, 1951.

113. Lebensohn, J. E.: Minus Lenses as an Effective Adjuvant in the Control of Juvenile Glaucoma, Am. J. Ophth. **35**:1029, 1952.

114. Kluyskens, J.: Congenital Glaucoma, Bull. Soc. belge opht. pp. 1-526, 1950.

115. Algan, B.: Treatment of Infantile Glaucoma, Nancy, Georges Thomas, 1951.

evidence of damage or corneal enlargement, goniotomy is the treatment of choice. However, iridencleisis, corneoscleral trephination, or cyclodiathermy may be used effectively. During the second stage, in which the eye begins to enlarge, goniotomy may be used if the angle can be visualized, but is risky if the angle cannot be seen. In the latter situation he mentions fistulizing operations as the ideal treatment. He occasionally uses cyclodiathermy as his operation of choice. In the third stage, in which the eyeball is markedly enlarged and the canal of Schlemm is obliterated, goniotomy is of no value. Fistulizing operations in these eyes may result in loss of vitreous, hemorrhage, or retinal detachment. At this stage he advocates either iridencleisis or cyclodiathermy, and in the fourth stage the choice rests between enucleation or cyclodiathermy. The author is of the opinion that cyclodiathermy should be used even in very late cases.

Increasing numbers of reports of favorable results obtained with goniotomy are appearing in the literature. Hertzberg [116] reviews the literature and concludes that goniotomy is the operation of choice for infantile glaucoma in eyes in which the corneal diameter is not over 15 mm. Of 115 cases collected from the literature (Barkan, Scheie, MacArevey), the tension had been normalized by goniotomy in 98. He reports three cases of his own in which the ocular tension was successfully controlled by goniotomy without a contact lens. Moore [117] performed goniotomy on both eyes of a 4-month-old baby. The tension in the left eye was normalized after the first procedure, but the operation had to be repeated on the right eye, and tension was finally controlled at the third operation by a goniopuncture. The tension then remained normal. Robertson [118] reports the results of goniotomy and/or goniopuncture in 11 eyes of seven patients. Goniotomy was done in eight eyes. In the other three first goniopuncture and then a combined goniotomy-goniopuncture operation were done. Success was encountered in 6 of the 11 eyes. The disease was far advanced in four of the five eyes in which failure occurred. Robertson concludes that when done early, goniotomy is the operation of choice in congenital glaucoma. If this fails, it is best to do either a goniopuncture or a combined goniotomy and goniopuncture as a second operation. Wilson,[119] in an excellent review article on congenital glaucoma, states that goniotomy is the operation of choice in congenital glaucoma. Scheie [120] reports further results in the treatment of infantile glaucoma by goniotomy, goniopuncture, and an operation which combines the two into a single procedure. In the combined operation a goniotomy is done, and upon completion of the sweep of the goniotomy knife the blade is pushed through the trabecular portion of the corneoscleral wall, but does not perforate the conjunctiva. The results in 17 eyes were reported. The tension was controlled, with preservation of vision, in 13—in 4 by goniotomy alone, in 5 by goniopuncture alone, and in 4 by a combination of goniotomy and goniopuncture. One eye reported

116. Hertzberg, R.: Goniotomy for Congenital Glaucoma: Review with Report of 3 Cases, M. J. Australia **2**:357, 1951.

117. Moore, M. C.: A Case of Buphthalmos Treated by Goniotomy, M. J. Australia **1**:800, 1951.

118. Robertson, E. N., Jr.: Surgical Treatment of Congenital Glaucoma, A. M. A. Arch. Ophth. **47**:611, 1952.

119. Wilson, W. A.: Congenital Glaucoma, Digest Ophth. & Otolaryng. **13**:703, 1951.

120. Scheie, H. G.: Management of Congenital Glaucoma, Tr. Pennsylvania Acad. Ophth. & Otolaryng. **4**:48, 1951.

in this paper as having the tension successfully controlled by cyclodiathermy has since undergone marked rise in tension. Three eyes were listed as having recently been reoperated on for increased tension, bringing the total number of failures to four. He concludes that goniotomy and goniopuncture are each effective as a primary procedure in the treatment of infantile glaucoma. Since goniotomy is effective through débridement of the angle and goniopuncture is a fistulizing procedure, it seems logical to combine the two procedures into one operation utilizing the advantages of each.

Troncoso [121] describes a new surgical contact lens with two windows for use in goniotomy; one is provided for fixation of the globe, and through the other the goniotomy knife can enter the anterior chamber. Laval [122] describes a procedure which he terms "goniotomy ab externo combined with iris inclusion"; in this he makes an incision at the limbus which cuts through the trabeculum, and a small piece of iris is incarcerated.

SECONDARY GLAUCOMA

1. *Uveitis.*—Glaucoma secondary to uveitis is the commonest type of secondary glaucoma. Several articles have appeared in the literature of the past year on the effect of cortisone in this type of secondary glaucoma. Crawford [123] reports a patient in whom the signs of uveitis and elevated ocular tension cleared under cortisone therapy. The visual acuity improved from 20/200 to 20/30. Wilson and Swift [124] report a similar experience with secondary glaucoma due to uveitis in a patient with rheumatoid disease. They quite logically state that cortisone is probably most beneficial in controlling inflammatory reaction and keeping the glaucoma under control while the basic cause of the disease subsides. Such a mechanism is much more probable than an effect upon the blood-aqueous barrier. Simonelli and Calamandrei [125] found that parenteral administration of 30 to 45 mg. of corticotropin for six to eight days caused no variation in permeability of the blood-aqueous barrier in normal subjects. Other reports of comparable results with even larger doses are recorded.

2. *Glaucoma Secondary to Herpes Zoster Ophthalmicus.*—Salomaa [126] states that glaucoma may result from herpes zoster ophthalmicus in two ways: It may occur as a result of herpetic iritis or, more rarely, as acute glaucoma with no signs of iritis. He found 14 cases of the latter type in the literature, but it would seem likely that these were really instances of true acute congestive glaucoma, a disease that we know can be precipitated by local irritation near or in the eye.

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121. Uribe Troncoso, M.: Surgical Treatment of Congenital Glaucoma, Am. J. Ophth. **35**:463, 1952.

122. Laval, J.: Operation for the Relief of Tension in Congenital Glaucoma, Goniotomy ab Externo Combined with Iris Inclusion, Am. J. Ophth. **35**:947, 1952.

123. Crawford, H. E.: Cortisone in Glaucoma Secondary to Uveitis, Am. J. Ophth. **34**:1320, 1951.

124. Wilson, E., and Swift, S. H.: Cortisone in Treatment of Secondary Glaucoma, M. J. Australia **2**:598, 1951.

125. Simonelli, M., and Calamandrei, G.: Behavior of Blood-Aqueous Barrier After Administration of Corticotropin, Gior. ital. oftal. **4**:340, 1951.

126. Salomaa, S.: Increased Intraocular Pressure Associated With Herpes Zoster Ophthalmicus Without any Signs of Iritis, Acta ophth. **29**:227, 1951.

3. *Syndrome of Glaucomatocyclitis Crises.*—There is no doubt as to the importance of this syndrome, which was first described by Posner and Schlossman in 1948. The disease is characterized by a rise in tension out of proportion to subjective symptoms or objective signs of cyclitis. In my experience, the diagnosis of cyclitis can easily be missed and is often made only after one or more attacks of what appeared to be acute congestive glaucoma with open angles. Posner [127] mentions the spontaneous normalization of tension and the fact that keratic precipitates may appear only one or two days after onset of the glaucoma. Topical use of cortisone seems to have a favorable effect. Posner states that surgical intervention does not prevent recurrences. Billet [128] reports the condition in a 50-year-old white man who gave a history of having at least 15 well-defined acute attacks of glaucoma over a period of seven years. He had had two previous operations, which had not prevented further attacks. Theodore,[129] in a review of the subject, discusses the importance of the syndrome and lists several characteristics of the disease, among which are the following: The pupil of the affected eye is larger than that of the unaffected eye. The diagnosis of uveitis is made only by slit-lamp examination. The elevation of tension is out of proportion to the symptoms. Recurrent attacks are the rule. The prognosis is good, and vision is not lost in spite of repeated attacks. Theodore emphasizes that this syndrome deserves a special place among glaucomas. It is definitely not primary glaucoma, and yet it cannot be dismissed as ordinary secondary glaucoma following uveitis because of the very unique picture which it presents. He mentions the possibility of allergy as a factor in such a self-limiting type of glaucoma. The temptation to operate should be resisted because these patients do not lose field or suffer visual impairment and attacks occur in the same manner as before surgery. Vanters' [130] article was very similar.

4. *Thrombosis of the Central Vein.*—Thrombosis of the central vein causes one of the most hopeless types of secondary glaucoma. Gutzeit [131] reports a case of thrombosis of the central vein and glaucoma which occurred coincidentally with tuberculosis of the pleura and peritoneum. Such an origin is rendered uncertain in view of the paper by Mancall [132] and of Verhoeff's discussion of the material when it was presented before the Section on Ophthalmology, American Medical Association, in 1951. They believe that in nearly all instances the central vein is closed as a result of endothelial proliferation, rather than of thrombosis. Verhoeff based his opinion on 200 eyes which he had studied.

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127. Posner, A.: Syndrome of Glaucomatocyclitic Crises, Eye, Ear, Nose & Throat Month. **31**:41, 1952.

128. Billet, E.: Syndrome of Glaucomatous Cyclitic Crisis, Am. J. Ophth. **35**:214, 1952.

129. Theodore, F. H.: Alterations of Glaucomatocyclitic Crises (Posner-Schlossman Syndrome), Brit. J. Ophth. **36**:207, (April) 1952.

130. Vanters, J.: A Little-Known Form of Hypertensive Uveitis: Recurrent Hypertensive Iridocyclitis; Presentation of 4 Cases, Bull. Soc. ophth. France, p. 695, June, 1951.

131. Gutzeit, R.: Thrombosis of the Central Retinal Vein and Hemorrhagic Glaucoma as Concomitant Conditions in a Tuberculous-Allergic Constitutional Disease, Klin. Monatsbl. Augenh. **117**:229, 1950.

132. Mancall, I. T.: Occlusion of the Central Retinal Vein: Ophthalmological Review, A. M. A. Arch. Ophth. **46**:668, 1951.

5. *Rubeosis Iridis.*—Zollinger [133] states that a sheet of new-formed vessels was invariably found on the surface of the iris in eyes with glaucoma secondary to occlusion of the central vein. This finding, however, is not specific, for it also occurs in diabetics, as indicated by François,[134] in the absence of occlusion of the central vein. In diabetics it is always complicated by secondary glaucoma. François [135] found, by gonioscopic examination, that the vascularization involved the root of the iris and extended onto the scleral trabeculum This probably led to subsequent fusion of the base of the iris with the corneoscleral wall. He questions whether such adhesions are the cause or the result of the hypertension. He emphasizes the unfavorable prognosis of the disease.

6. *Uveal-Pigment Disturbances.*—Additional reports on glaucoma associated with pigmentary degeneration of the uveal tract have appeared. Carter [136] reports a case of glaucoma, associated with early atrophy of the iris, occurring in a 36-year-old woman. Van Beuningen [137] reported two instances of progressive atrophy of the iris stroma, one in an 11-year-old girl and another in a 46-year-old woman.

7. *Diseases of the Lens.*—(*a*) Glaucoma Capsulare: Loewenstein,[138] after studying patients with glaucoma associated with exfoliation of the lens capsule, concludes that shreds of lens capsule deposited in the trabeculum obstruct the outflow of aqueous, and he therefore places this disease in the category of secondary glaucoma. Bhaduri [139] arrives at a similar conclusion. Weekers, Weekers, and Dedoyard,[140] on the other hand, are of the opinion that the increased ocular tension is not the result of obstruction of the canal.

(*b*) Endophthalmitis Phacoanaphylactica: Irvine and Irvine,[141] in an excellent series of articles, show that the lens may produce inflammatory responses of at least three general types: the phacoanaphylactic response, the toxic response, and the phacogenetic response. The mechanism of each type is discussed. Macrophages may block the angle meshwork, causing the glaucoma in many instances. In the fellow eye a similar iridocyclitis may develop as a result of leakage of lens substance into the ocular cavity, but this is always accompanied by a hypermature cataract. The glaucoma and the inflammation can often be cured and the eye saved by washing out the lens protein.

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133. Zollinger, R.: New Formation of Vessels on the Iris: A Histological Study, Ophthalmologica **121**:168, 1951.

134. François, J.: Rubeosis of the Iris, Ophthalmologica **121**:313, 1951.

135. François, J.: Gonioscopy in Rubeosis Iridis, Bull. Soc. opht. France **63**:223, 1950.

136. Carter, L. F.: Progressive Essential Atrophy of the Iris, Am. J. Ophth. **35**:522, 1952.

137. van Beuningen, E. G. A.: Vergleichende gonioskopische Untersuchungen fortschreitender, nichtdurchgreifender Irislochbildungen, Klin. Monatsbl. Augenh. **119**:279, 1951.

138. Loewenstein, A.: The Anterior Draining System in the Human Eye, Ophthalmologica **122**:257, 1951.

139. Bhaduri, B. N.: Senile Exfoliation of the Lens Capsule, Proc. All-India Ophth. Soc. **10**:55, 1949.

140. Weekers, L.; Weekers, R., and Dedoyard, J.: Pathogenesis of "Capsular" Glaucoma, Docum. ophth. **5-6**:555, 1951.

141. Irvine, S. R., and Irvine, A. R.: Lens-Induced Uveitis and Glaucoma: I. Endophthalmitis Phaco-anaphylactica, Am. J. Ophth. **35**:177, 1952; Lens-Induced Uveitis and Glaucoma: II. The "Phacotoxic" Reaction, ibid. **35**:370, 1952; Lens-Induced Uveitis and Glaucoma: III. "Phacogenetic Glaucoma," ibid. **35**:489, 1952.

(*c*) Glaucoma Secondary to Cataract Surgery: The incidence of glaucoma following cataract extraction is continually being reduced as a result of improved methods of wound closure. Townes and associates,[142] reviewing 565 cases of cataract extraction, found that glaucoma developed in 33; in 17 of these surgery was required, and cyclodialysis was chosen. Gördüren and Tosunoğlu [143] report a case of glaucoma following extracapsular cataract extraction due to epithelial downgrowth. The condition was apparently arrested and the ocular tension controlled by x-ray therapy.

8. *Trauma.*—Glaucoma secondary to traumatic hyphema is a very serious ophthalmologic problem. Thygeson and Beard,[144] in their 34 cases, noted that glaucoma did not develop in any in which there was but a single hemorrhage. However, of 13 cases of secondary hemorrhage, secondary glaucoma developed in 7. When operation was required because of the increased ocular tension, the results were very poor. Of the seven cases in which operation was required, enucleation was necessary in 2; the eye was blind in one; vision was limited to light perception in two, and 20/60 vision was obtained in one and 20/30 vision in the other. When secondary glaucoma did not occur, the visual results were good. The authors outline their method of treatment.

9. *Myopia.*—Bedrossian [145] divides myopia into the pathologic and the nonpathologic types. According to his classification, the pathologic type is any myopia in which there is associated some disease of the eye, such as vitreal changes, uveitis, or choroidal or retinal changes. He points out that glaucoma may be associated with the pathologic types of myopia, such as low-grade uveitis; that in other instances myopia may be secondary to glaucoma, and that in still others the two situations may be mixed. It is Bedrossian's opinion that glaucoma may be the cause of progressive myopia in certain instances, and he quite properly emphasizes the need for careful studies to rule out the presence of glaucoma in all eyes with progressive myopia.

142. Townes, C. D.; Moran, C. T., and Pfingst, H. A.: Complications of Cataract Surgery, Tr. Am. Ophth. Soc. **49**:91, 1951.

143. Gördüren, S., and Tosunoğlu, K.: Epithelial Invasion of the Anterior Chamber, Göz. Klin. **9**:27, 1951.

144. Thygeson, P., and Beard, C.: Observations on Traumatic Hyphema, Am. J. Ophth. **35**:977, 1952.

145. Bedrossian, E. H.: Progressive Myopia with Glaucoma, Am. J. Ophth. **35**:485, 1952.

News and Comment

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Stanford University School of Medicine Annual Postgraduate Conference in Ophthalmology.—The Stanford University School of Medicine will present the annual postgraduate conference in clinical ophthalmology from March 23 through 27, 1953. The program this year will be devoted to ophthalmic surgery. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye or of the eye, ear, nose, and throat. In order that free discussion may be available to members of the conference, registration will be limited to 30 physicians.

Instructors will be Dr. A. Edward Maumenee, Dr. Dohrmann K. Pischel, Dr. Jerome W. Bettman, Dr. Max Fine, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Programs and further information may be obtained from the Office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

Course in Ophthalmology for Specialists, University of Minnesota.—The University of Minnesota will present a continuation course in ophthalmology for specialists at the Center for Continuation Study from Jan. 19 to 24, 1953. Emphasis will be placed throughout the session on therapy of a variety of ocular disorders.

The visiting faculty for the course will include Dr. Kenneth C. Swan, professor and head, Department of Ophthalmology, University of Oregon Medical School, Portland. The course will be presented under the direction of Dr. Erling W. Hansen, professor and director, Division of Ophthalmology, and the remainder of the faculty will include members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

Fifth Pan-American Congress of Ophthalmology.—The Fifth Pan-American Congress of Ophthalmology will be held at Santiago, Chile, in February, 1956. The exact date will be announced later.

The Chilean Society of Ophthalmology has designated the following officers for the Congress: president, Dr. Cristobal Espildora; vice-president, Dr. Santiago Barrenechea; secretary-general, Dr. Rene Contardo, Huerfanos 930, Of. 74, Santiago, Chile, and treasurer, Dr. Abraham Schweitzer.

Annual Clinical Conference at Wills Hospital.—The fifth annual clinical conference of the staff and ex-residents of Wills Hospital will be held on March 20 and 21, 1953, in Philadelphia.

The Arthur J. Bedell Lecture will be delivered by Dr. John H. Dunnington, of New York.

SOCIETY NEWS

Ophthalmological Society of Australia.—The thirteenth annual general meeting of the Ophthalmological Society of Australia will be held at Adelaide, South Australia, in the week commencing Oct. 12, 1953. Dr. A. L. Tostevin, of Adelaide, is president of the society, and Dr. Arnold L. Lance is secretary.

Georgia Society of Ophthalmology and Otolaryngology.—The Georgia Society of Ophthalmology and Otolaryngology will hold its spring meeting at the General Oglethorpe Hotel in Savannah, Ga., on March 6 and 7, 1953. The following outstanding and internationally known teachers will be the speakers: Dr. Peter C. Kronfeld, Chicago; Dr. Edmund B. Spaeth, Philadelphia; Dr. Frank B. Walsh, Baltimore; Dr. Louis H. Clerf, Philadelphia; Dr. Edmund P. Fowler Jr., New York, and Dr. Theo E. Walsh, St. Louis. Reservations should be made through correspondence with the hotel, but for any other desired information, write the secretary of the Society, Dr. Alton V. Hallum, 245 Doctors Building, Atlanta 3, Ga.

Books

Ophthalmic Plastic Surgery. By Sidney A. Fox, M.D. Price, $15. Pp. 290, with 133 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

This practical book on plastic surgery is valuable because the author has made no attempt to present the numerous procedures found in the literature, but has included only those techniques which he has personally used and which have proved satisfactory over a period of time. Only too often surgical texts have become storehouses for operations which were hastily documented in the literature in the enthusiasm engendered by one successful case. The author subsequently discovers that further experience with the method results in unforeseen complications and drops the method, wishing at the same time that he had not so hastily rushed into print. Alas, the writer of a textbook has picked it up out of the current literature and endowed it with permanence.

The procedures which Dr. Fox advocates are described in clear and concise terms. Emphasis has been placed on illustrations rather than on words, in obedience to the old Chinese proverb. The illustrations are excellent, and the whole make-up of the book leaves nothing to be desired. Chapter I describes the anatomy of the brow and the lids. Chapter II presents the fundamentals of lid surgery. Chapter III is a general review of skin grafting. Chapter IV deals with technical details, such as the preparation of the patient, asepsis, instruments, and anesthesia. Minor surgical procedures, such as canthoplasty, repair of epicanthus (some surgeons might not consider this so minor), and operations for xanthelasma, are dealt with in Chapter V. The next 12 chapters deal with specific problems in plastic surgery, covering all the surgery of the lids, displacements of the globe, surgery of the conjunctiva, and socket reconstruction. A good bibliography follows each chapter.

Ophthalmic Glossary. By M. R. Goldman, M.D. Price, $2.50. Pp. 40. Richard Rimbach Associates, 921 Ridge Ave., Pittsburgh 12.

This glossary has little to recommend it. The reviewer has seldom seen a book with so many gross errors. A few examples will suffice to illustrate:

> The definition of chloroform is given as follows: "Cysts of cornea after use of . . ."
> Morgagnian cataract: "Has hard brown nucleus and does not liquefy."
> Myotonia atrophica (Steinert's disease): "Cataractous lens changes."
> Law, Sherrington's: "All muscles remain in slight stage of tonicity, with relaxation and contraction in the execution of a movement."
> Glare: "Diffusion of light over retina instead of sharp focus."

There are numerous examples of misspelling. In the words of the author, this glossary was intended primarily not for the ophthalmologist but for the general practitioner, medical secretary, social service worker, optician and optometrist, and those of the laity who may need information on the terminology of ophthalmology. It would seem that such persons seeking help could find a more authoritative source.

Estrabismos. First edition. By Alfonso Castanera Pueyo. Price, 200 pesetas. Pp. 300, with 90 illustrations. Editorial Paz Montalvo, General Goded 19, Madrid, 1952.

This book on strabismus comes to fill a vacuum in the Spanish ophthalmologic literature, presenting in one volume a summary of the great quantity of papers,

publications, and conferences on the subject in many languages. The well-organized context and the simple, clear presentation of the present fundamental concepts regarding the physiology of vision and the motor system, the etiology of strabismus, and its classification, diagnosis, and treatment should prove of great value to the student and practitioner of ophthalmology.

The first three chapters cover the anatomy, physiology, and pathology of the oculomotor apparatus. Functional pathology is broken down into alterations of the static eye—position of eyes modified by anatomical structure of the glove, muscles, or orbit—and dynamic alterations—deficiency of action or overaction of one or more muscles. Chapters IV and V present the development of monocular and binocular vision and the sensory disturbances that occur in strabismus.

The second part of the book begins with a classification of the etiologic factors and the various theories of origin of squint—unitarian and mixed. The next few chapters contain a classification of squint, a discussion and description of the necessary elements or equipment for diagnosis and treatment of strabismus, the importance of the case history and the findings, the complete examination of the motor and sensory status, and the evaluation of fusion.

A chapter is devoted to a description of the synoptophore and its use in the diagnosis. The last three chapters present Dr. Castanera's procedure for treatment of strabismus, including general measures, orthoptic training, and surgical correction.

Biomicroscopie et histopathologie de l'oeil. By Archimede Busacca, M.D. Price, $35. Pp. 480, with 221 illustrations. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1952.

This is a beautifully illustrated text in French presenting the histological basis for the lesions of the eye which are seen with the biomicroscope. The colored illustrations are superb and make the book extremely valuable for even those who do not read French. This book is Volume I of a set and deals specifically with lesions of the conjunctiva and the cornea. It does not deal with the technique of biomicroscopy or the principles of biomicroscopy, but assumes that the reader is already acquainted with the use of this instrument.

The author and the publishers are to be congratulated on having produced such a beautiful volume. A translation into English would make the book even more valuable for use in the United States.

CORRECTION

In the article entitled "A Simplified Blaskovics Operation for Blepharoptosis," by Dr. Raynold N. Berke, published in the October issue, the references to the figures on page 476 were incorrect. "Figure 24" should have read "Figure 25," and "Figure 25" should have read "Figure 26."

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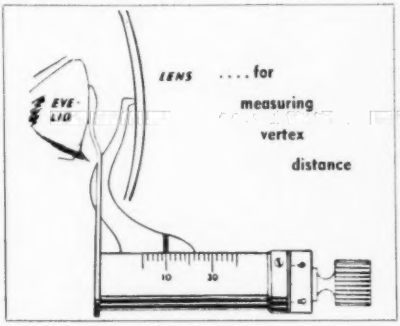

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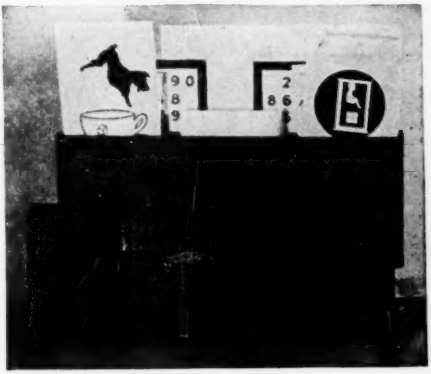

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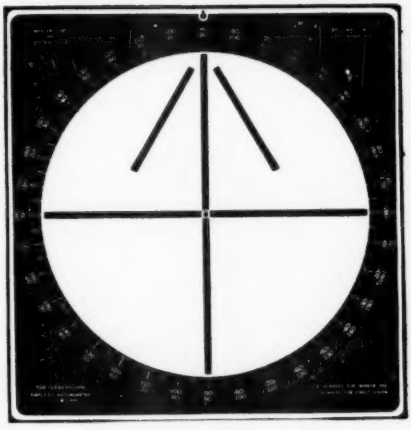

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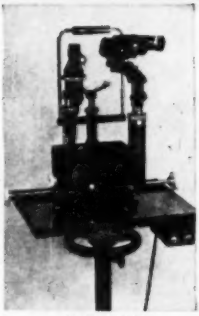

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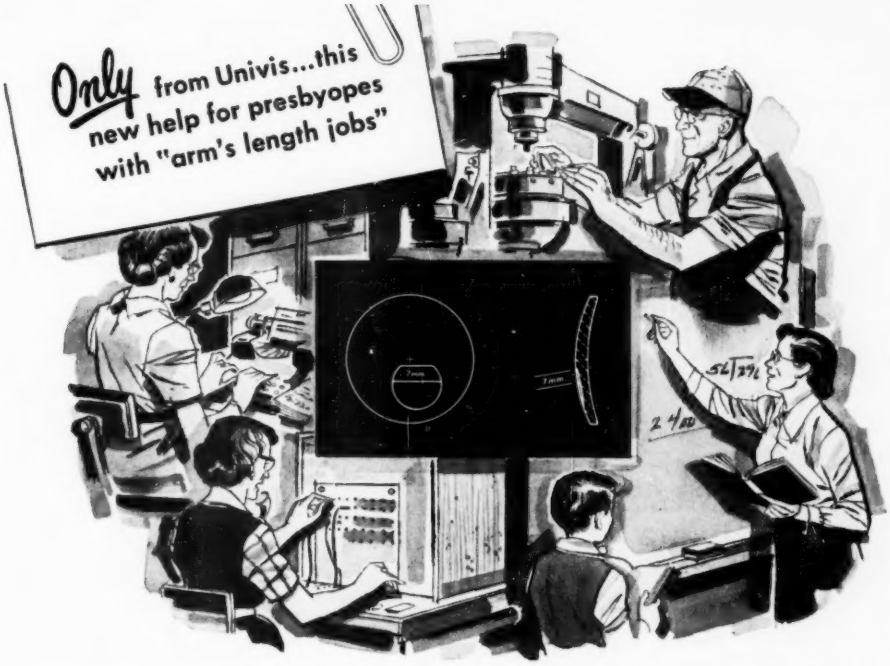

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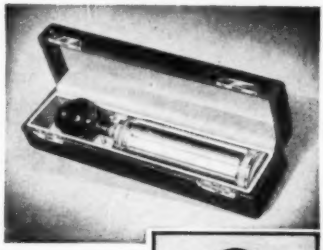

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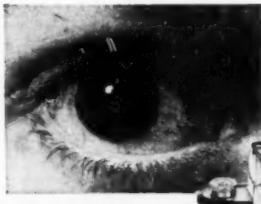

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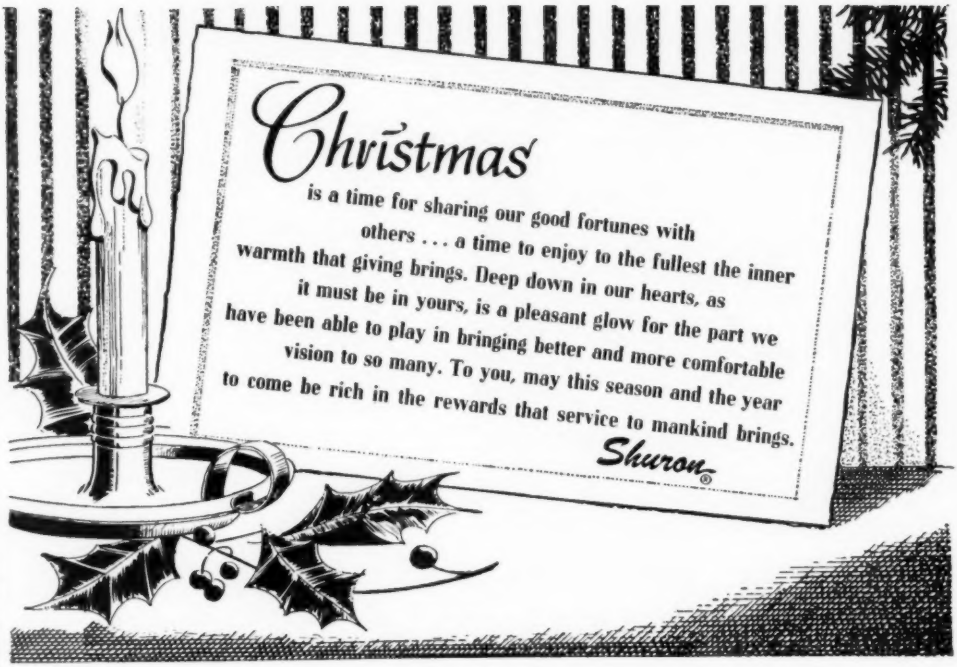
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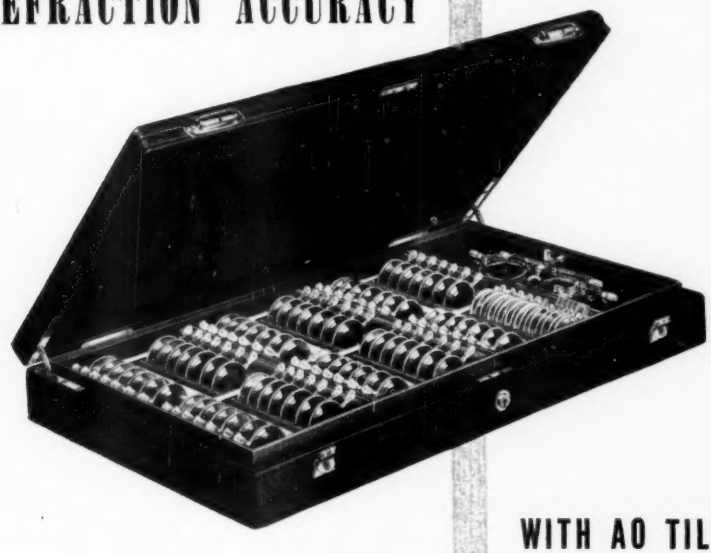

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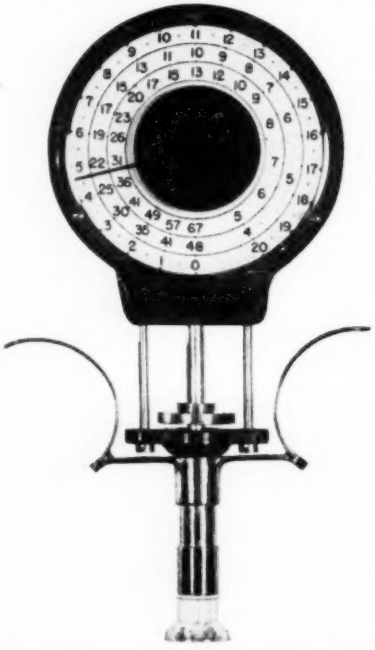

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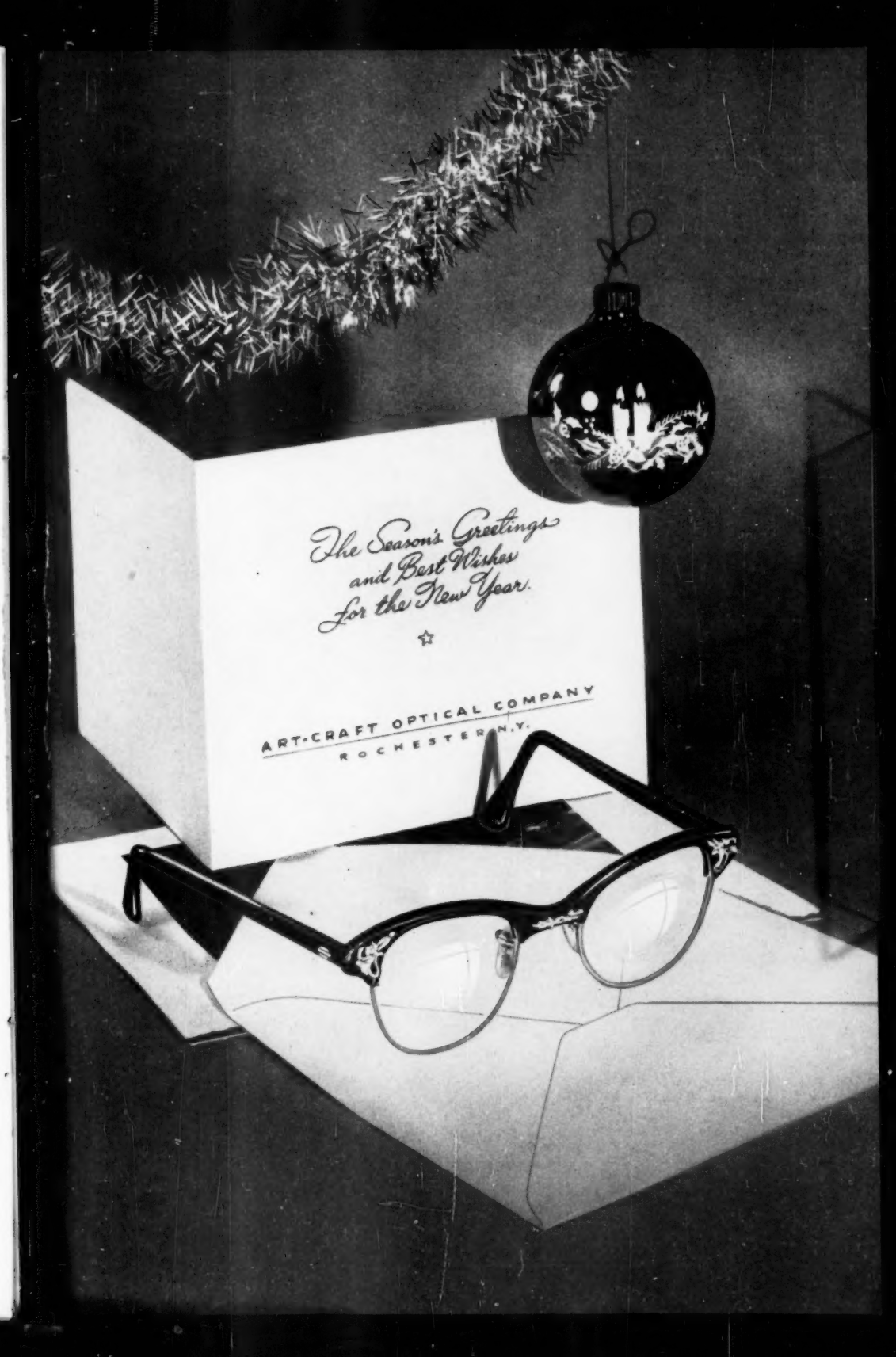
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